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12 UNITED STATES DISTRICT COURT
13 EASTERN DISTRICT OF WASHINGTON

14 STATE OF WASHINGTON, et al.,
15 Plaintiffs,
16 v.

17 UNITED STATES FOOD AND DRUG
18 ADMINISTRATION, et al.

19 Defendants,

20 STATE OF IDAHO; STATE OF
21 IOWA; STATE OF MONTANA;
22 STATE OF NEBRASKA; STATE OF
23 SOUTH CAROLINA; STATE OF
24 TEXAS; STATE OF UTAH,

Plaintiffs-Intervenors,

Case No. 1:23-cv-03026

COMPLAINT

INTRODUCTION

1
2 1. On September 28, 2000, the U.S. Food and Drug Administra-
3 tion (FDA) determined that mifepristone was unsafe for marketing and
4 use without important restrictions that were designed to mitigate the se-
5 rious dangers posed by the drug.

6 2. For 23 years, one of those restrictions was that a certified
7 health care provider needed to dispense mifepristone to patients in per-
8 son in a clinical setting.

9 3. This common-sense safety measure was deemed necessary by
10 the FDA to protect women from the drug's deadly potential.

11 4. Yet the FDA under the Biden administration has suddenly
12 determined that mifepristone no longer needs to be dispensed in person.
13 On January 23, 2023, the FDA eliminated mifepristone's in-person dis-
14 pensing requirement.

15 5. The FDA made this substantive change without providing the
16 notice and opportunity to comment required by the Administrative Pro-
17 cedure Act, 5 U.S.C. § 553.

18 6. The FDA also did not sufficiently justify its drastic decision.
19 Nor could it. Nothing about the drug's danger has changed. And nothing
20 else relevant has changed that would alter the risk-benefit profile the
21 FDA has consistently determined requires in-person dispensing.

22 7. This final agency action harms women in Idaho, Iowa, Mon-
23 tana, Nebraska, South Carolina, Texas, and Utah; it will undermine
24 state law; and it is a violation of federal law. The FDA's unilateral deci-
sion to eliminate mifepristone's in-person dispensing requirement did not
provide required notice and an opportunity for public comment, was ar-
bitrary and capricious, and exceeded the FDA's authority under the Food,

1 Drug, and Cosmetic Act, all in violation of the APA.

2 JURISDICTION AND VENUE

3 8. This Court has jurisdiction pursuant to 28 U.S.C. § 1331 be-
4 cause this action raises federal questions under the Administrative Pro-
5 cedures Act, 5 U.S.C. §§ 551(13), 702, and 704, and the Food, Drug, and
6 Cosmetic Act (FDCA), 21 U.S.C. § 301 *et seq.*

7 9. This Court also has jurisdiction to declare the law, enjoin the
8 FDA's unlawful final action, invalidate the FDA's final action, and pro-
9 vide further necessary or proper relief pursuant to 28 U.S.C. §§ 2201 and
10 2202. There is a real and present controversy between the parties regard-
ing the lawfulness of the FDA's final action.

11 10. Venue is proper in this Court pursuant to 28 U.S.C.
12 § 1391(e)(1)(C) because Defendants are agencies of the United States or
13 officers or employees of the United States acting in their official capaci-
ties and Plaintiff State of Washington resides in this district.

14 PARTIES

15 11. Plaintiffs State of Idaho, State of Iowa, State of Montana,
16 State of Nebraska, State of South Carolina, State of Texas, and State of
17 Utah, by and through their Attorneys General, bring this suit to assert
18 their rights as Sovereign States and on behalf of their citizens. *See* Idaho
19 Const. art. IV, § 1; Idaho Code §67-1401(1), (2), and (15); Iowa Const. art.
20 V, § 12; Iowa Code Ann. § 13.2; Mont. Const. art. VI, § 4(4); Mont. Code
21 Ann. § 2-15-501; Neb. Const. art. V, § 1; Neb. Rev. Stat. § 84-203 S.C.
22 Const. art. V, § 24; S.C. Code § 1-7-40; Tex. Const. art. IV, § 22; Tex. Gov't
Code Ch. 402; Utah Const. art. VII, § 16; Utah Code § 67-5-1.

23 12. Separate Plaintiffs Washington, Oregon, Arizona, Colorado,
24

1 Connecticut, Delaware, Illinois, Nevada, New Mexico, Rhode Island, Ver-
2 mont, and the Michigan Attorney General are existing Plaintiffs in this
3 suit.

4 13. Defendant United States Food and Drug Administration is an
5 agency within the United States Department of Health and Human Ser-
6 vices (HHS). The FDA is responsible for administering the provisions of
7 the FDCA for approving new drug applications and authorizing a Risk
8 Evaluation and Mitigation Strategy (REMS) for drugs, like mifepristone,
that pose serious safety concerns.

9 14. Defendant Robert M. Califf, Commissioner of the FDA, is re-
10 sponsible for administering the FDA and overseeing its duties under the
11 FDCA, including the issuance and modification of REMS. Plaintiffs sue
12 him in his official capacity.

13 15. Defendant HHS is a federal agency that has statutory author-
14 ity under the FDCA and has delegated that authority to Defendant FDA
15 to administer the provisions of the FDCA that are relevant to this Com-
plaint.

16 16. Defendant Xavier Becerra, Secretary of HHS, is responsible
17 for the operations of HHS, including overseeing the FDA. Plaintiffs sue
18 him in his official capacity.

BACKGROUND

The History of Mifepristone and Its Marketing Requirements

17. Before a drug can be approved for marketing, the FDA must determine that the drug is “safe for use,” meaning that the drug’s expected benefits outweigh its potential risks. 21 U.S.C. § 355; *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 140 (2000).

18. Some drugs are so risky, and pose significant enough dangers, that the FDA requires drug makers to develop programs for their safe use. *See* 21 U.S.C. § 355-1.

19. For these drugs to receive FDA approval, the FDA requires a REMS “to ensure that the benefits of the drug outweigh the risks of the drug.” 21 U.S.C. § 355-1(a)(1).

20. In September 2000, the FDA determined that mifepristone could not be approved for marketing without “restrictions to assure safe use” under Subpart H of the FDCA (which later were deemed to be an approved REMS under the Food and Drug Administration Amendments Act).

21. Mifepristone is an endocrine disruptor that blocks progesterone receptors in the uterus. Progesterone is necessary for the development of an unborn child and the normal maintenance of a pregnancy. Thus, when ingested by a pregnant woman, mifepristone blocks nutrition to the unborn child and starves it.

22. Mifepristone, however, does not work alone. Another drug, misoprostol, is needed to induce uterine contractions and expel the dead or dying unborn child from the womb.

23. The FDA requires mifepristone to be used in a regimen with misoprostol.

1 24. Mifepristone’s FDA-approved label warns—in large, bolded
2 text—that “[s]erious and sometimes fatal infections and bleeding occur
3 very rarely following” use of mifepristone.

4 25. This “black box warning” was necessary because the FDA de-
5 termined that mifepristone poses “special problems, particularly those
6 that may lead to death or serious injury.”

7 26. Due to these “special problems,” the FDA approved the drug
8 only with the following restrictions:

- 9 a. Mifepristone regimen must be dispensed and administered in
10 person in a hospital, clinic, or medical office by, or under the
11 supervision of, a certified provider.
12 b. Mifepristone regimen must be prescribed by a certified health
13 care provider.
14 c. Mifepristone regimen must be dispensed to patients with evi-
15 dence or other documentation of safe use conditions as en-
16 sured by the certified prescriber in signing the Prescriber
17 Agreement Form and by the patient signing the Patient
18 Agreement Form.

19 27. These restrictions are referred to as Elements to Assure Safe
20 Use (ETASUs).

21 28. Initially, mifepristone was approved for use only up to 49
22 days’ gestation. In 2016, the FDA increased the gestational age limit to
23 70 days.

24 29. The increased period of use, however, made the in-person dis-
25 pensing requirement even more important and necessary.

 30. Hence, the FDA continued to require the in-person dispensing
of the drug in an appropriate clinic setting, prescribed by a certified

1 health care provider, with evidence, through execution of the Prescriber
2 Agreement Form and Patient Agreement Form, that the patient was
3 properly informed of the risks.

4 31. On January 3, 2023, the FDA made major modifications to
5 mifepristone's REMS by eliminating the in-person dispensing require-
6 ment. It nevertheless determined that mifepristone remains a dangerous
7 drug requiring a REMS and ETASUs.

8 32. The FDA made this substantive change without following the
9 APA's notice and comment procedures.

10 33. The FDA also failed to adequately explain or support elimi-
11 nating the in-person dispensing requirement, which it had previously de-
12 termined was required for safe use. Instead, in its December 16, 2021
13 letter noticing the modification, the FDA simply parroted the statutory
14 language that the mifepristone REMS program "must be modified to min-
15 imize the burden on the health care delivery system of complying with
16 the REMS and to ensure that the benefits of the drug outweigh the risks."
17 (Ex. 1.)

18 34. This conclusory assertion provides no explanation of how
19 eliminating the in-person dispensing requirement would minimize the
20 burden on the health care delivery system or how it would ensure that
21 the drug's benefits outweigh its risks. The FDA letter cites no studies,
22 contains no data, identifies no factors or considerations relevant to its
23 determination, and fails to explain what scientific, medical, or other
24 changes justify eliminating the in-person dispensing requirement that it
had insisted upon for the first 23 years of the drug's existence.

35. On the same day that the FDA conclusorily noticed eliminat-
ing the in-person dispensing requirement for mifepristone, it responded

1 by letter to a citizen petition submitted to the FDA on March 29, 2019.
2 The citizen petition specifically requested the FDA to retain the in-person
3 dispensing requirement. The FDA's response was lengthy but devoid of
4 the necessary support to justify elimination of the in-person dispensing
5 requirement. In fact, the FDA admitted in its response letter that elimi-
6 nating the in-person dispensing requirement was shown by studies to re-
7 sult in "an increase in ED/urgent care visits." The FDA further acknowl-
8 edged that there was "insufficient data" to "determine the safety and ef-
9 ficacy of dispensing from a retail pharmacy, by courier, or by a partner
10 organization." (Ex. 2.)

11 36. The FDA's December 16, 2021 response to the citizen peti-
12 tion—and specifically its rejection of the citizen petition's request to re-
13 tain the in-person dispensing requirement—demonstrates that the
14 FDA's position on eliminating the in-person dispensing requirement was
15 "already set" and "very likely" that any petition by the States opposing
16 the elimination would be rejected by the FDA. *El Rescate Legal Servs.,*
17 *Inc. v. EOIR*, 959 F.2d 742, 747 (9th Cir. 1991) (citation omitted). Thus,
18 resorting to agency administrative remedies would have been futile. *Id.*

19 37. The bottom line is that the FDA failed to consider relevant
20 data, such as scientifically acceptable studies or relevant sources of in-
21 formation, and it identified no change to the risk profile of mifepristone.

22 38. In fact, nothing relevant has changed to justify the FDA's
23 elimination of the in-person dispensing requirement. The FDA's action is
24 attributable to the change to the new Biden administration, not new med-
ical or scientific evidence.

The FDA's Action Harms Idaho and its Residents

39. Idaho is principally responsible for ensuring the safety of its citizens.

40. Idaho also has “legitimate interests” in the “respect for and preservation of prenatal life at all stages of development.” *Dobbs v. Jackson Women’s Health Org.*, 142 S. Ct. 2228, 2284 (2022).

41. The FDA’s decision to eliminate mifepristone’s in-person dispensing requirement will harm Idaho women and prenatal life.

42. As the FDA readily acknowledges, mifepristone is a dangerous drug that can cause death or serious bodily harm.

43. The 23-year requirement that mifepristone be prescribed and administered in person in a clinical setting by a certified health care provider was a sensible, necessary requirement to assure the drug’s safe use.

44. Taking mifepristone—even as prescribed—can cause death or serious bodily harm requiring immediate medical attention.

45. Without the in-person dispensing requirement, women in Idaho will be exposed to the dangerous complications caused by the drug and will be left without any professional medical oversight or prompt medical assistance.

46. Taking mifepristone when contraindicated increases the likelihood of death or serious bodily harm.

47. Without the in-person dispensing requirement, women in Idaho who do not meet the indications for use will be able to take mifepristone. In other words, the in-person dispensing requirement is a necessary feature to ensure that women with contraindications don’t take mifepristone.

1 48. For example, women with ectopic pregnancies cannot be pre-
2 scribed mifepristone. But in-person medical care and in-person dispens-
3 ing are crucial safety measures to accurately diagnose an ectopic preg-
4 nancy. It is particularly dangerous for a woman with an ectopic preg-
5 nancy to take mifepristone because the drug masks the symptoms of a
6 ruptured ectopic pregnancy.

7 49. Taking mifepristone beyond the approved-for-use 70-day ges-
8 tational period increases the likelihood of death or serious bodily harm.

9 50. Without the in-person dispensing requirement, important
10 safeguards will no longer protect women in Idaho from being adminis-
11 tered the drug outside of the 70-day gestational limitation.

12 51. The in-person dispensing requirement is the safest and surest
13 way to protect women from being administered mifepristone beyond the
14 70-day gestational period.

15 52. Idaho also has a sovereign interest in ensuring that its laws
16 are enforced and not undermined. *See Alfred L. Snapp Son, Inc. v. Puerto*
17 *Rico ex rel. Pedro Barez*, 458 U.S. 592, 601 (1982). Idaho law protects
18 women and prenatal life from abortion-inducing drugs like mifepristone.
19 *See Idaho Code* §§ 18-602 (recognizing “[t]hat children have a special
20 place in society that the law should reflect”), 18-617 (defining “Abortifa-
21 cient” to mean “mifepristone, misoprostol and/or other chemical or drug
22 dispensed with the intent of causing an abortion”), and 18-622 (“Every
23 person who performs or attempts to perform an abortion as defined in
24 this chapter commits the crime of criminal abortion.”). But the FDA’s
elimination of the in-person dispensing requirement will undermine
Idaho’s ability to enforce its laws. Specifically, without the in-person dis-
pensing requirement, mifepristone will be able to travel across Idaho’s

1 borders and be used to unlawfully induce abortions in Idaho. Mifepris-
2 tone will no longer be subject to the controlled delivery system that the
3 FDA had always required and deemed necessary. Under the FDA's new
4 rule, for example, a health care provider in Washington could conduct a
5 telehealth appointment with an Idaho resident and prescribe her mife-
6 pristone. Further, an Idaho resident could travel to Washington to have
7 a mifepristone prescription filled by a pharmacy in Washington and re-
8 turn to Idaho with mifepristone. Each of these scenarios will result in an
9 influx of mifepristone in Idaho, with no safeguards to prevent the drug
10 from freely circulating and being administered unlawfully and improp-
erly.

11 53. Under the FDA's new rule, women and unborn children in
12 Idaho will also be put at increased risk. The elimination of the in-person
13 dispensing requirement further removes women from medical care nec-
14 essary to protect them from the dangerous potential of mifepristone. And
15 the elimination of the in-person dispensing requirement will also endan-
16 ger unborn children in Idaho by making it more likely that such children
17 who are protected by Idaho law or who are too old to "safely" be aborted
by the drug are nevertheless subjected to the drug's fatal effects.

18 54. The increased risk to Idaho women and unborn children will
19 further harm Idaho by causing it to incur additional medical care ex-
20 penses, including emergency care, some of which is borne by Idaho
21 through Medicaid expenditures. As the FDA recognized, elimination of
22 the in-person dispensing requirement has been shown to result in more
emergency and urgent care visits.

23 55. The longstanding in-person dispensing requirement has also
24 created reliance interests for Idaho. Effective enforcement of Idaho's law

1 and protection of Idaho women and unborn children has been built
2 around and depends on mifepristone's REMS—including an in-person
3 dispensing requirement.

4 56. Idaho thus has both quasi-sovereign and sovereign interests
5 that are harmed by the FDA's decision to eliminate mifepristone's in-per-
6 son dispensing requirement.

7 ***The FDA's Action Harms Iowa and its Residents***

8 57. Iowa is principally responsible for ensuring the safety of its
9 citizens.

10 58. Iowa also has "legitimate interests" in the "respect for and
11 preservation of prenatal life at all stages of development." *Dobbs v. Jack-*
12 *son Women's Health Org.*, 142 S. Ct. 2228, 2284 (2022).

13 59. The FDA's decision to eliminate mifepristone's in-person dis-
14 pensing requirement will harm Iowa women and prenatal life.

15 60. As the FDA readily acknowledges, mifepristone is a danger-
16 ous drug that can cause death or serious bodily harm.

17 61. The 23-year requirement that mifepristone be prescribed and
18 administered in person in a clinical setting by a certified health care pro-
19 vider was a sensible, necessary requirement.

20 62. Taking mifepristone—even as prescribed—can cause serious
21 bodily harm requiring immediate medical attention or death.

22 63. Without the in-person dispensing requirement, women in
23 Iowa will be exposed to the dangerous complications mifepristone may
24 cause and will be left without any professional medical oversight or
prompt medical assistance.

64. Taking mifepristone when contraindicated increases the like-
lihood of death or serious bodily harm.

1 65. Without the in-person dispensing requirement, women in
2 Iowa who do not meet the indications for use will be able to take mife-
3 pristone. In other words, the in-person dispensing requirement is a nec-
4 essary feature to ensure that women with contraindications don't take
5 mifepristone.

6 66. Taking mifepristone beyond the approved-for-use 70-day ges-
7 tational period increases the likelihood of death or serious bodily harm.

8 67. Without the in-person dispensing requirement, important
9 safeguards will no longer protect women in Iowa from being administered
10 the drug outside of the 70-day gestational limitation.

11 68. The in-person dispensing requirement is the safest and surest
12 way to protect women from being administered mifepristone beyond the
13 70-day gestational period.

14 69. Iowa has a sovereign interest in ensuring that its laws are
15 enforced and not undermined. *See Alfred L. Snapp Son, Inc. v. Puerto*
16 *Rico ex rel. Pedro Barez*, 458 U.S. 592, 601 (1982). But the FDA's elimi-
17 nation of the in-person dispensing requirement will undermine Iowa's
18 ability to enforce its laws. Specifically, without the in-person dispensing
19 requirement, mifepristone will be able to travel across Iowa's borders and
20 potentially violate state or federal law to unlawfully induce abortions in
21 Iowa. Mifepristone will no longer be subject to the controlled delivery sys-
22 tem that the FDA had always required and deemed necessary.

23 70. Under the FDA's new rule, women and unborn children in
24 Iowa will also be put at increased risk. The elimination of the in-person
dispensing requirement further removes women from medical care nec-
essary to protect them from the potentially dangerous mifepristone. And

1 the elimination of the in-person dispensing requirement will also endan-
 2 ger unborn children in Iowa by making it more likely that such children
 3 who may be too old to “safely” be aborted by the drug are nevertheless
 4 subjected to the drug’s fatal effects.

5 71. The longstanding in-person dispensing requirement has also
 6 created reliance interests for Iowa. Effective enforcement of Iowa’s law
 7 and protection of Iowa women and unborn children has been built around
 8 and depends on mifepristone’s REMS—including an in-person dispens-
 9 ing requirement.

10 72. Iowa thus has both quasi-sovereign and sovereign interests
 11 that are harmed by the FDA’s decision to eliminate mifepristone’s in-per-
 12 son dispensing requirement.

12 ***The FDA’s Action Harms Montana and its Residents***

13 73. Montana has a sovereign interest in ensuring that its laws are
 14 enforced and not undermined. *See Alfred L. Snapp Son, Inc. v. Puerto*
 15 *Rico ex rel. Pedro Barez*, 458 U.S. 592, 601 (1982). Montana law protects
 16 women from abortion-inducing drugs like mifepristone. *See* Mont. Code
 17 Ann. § 50-20-702(1) (recognizing a compelling state interest in “protect-
 18 ing the health and welfare of a woman considering a chemical abortion”);
 19 *id.* § 50-20-703(2) (defining “[a]bortion-inducing drug” or “chemical abor-
 20 tion” as drugs with “abortion-inducing properties” that are “prescribed
 21 specifically with the intent of causing an abortion,” including “mifepris-
 22 tone, misoprostol, and methotrexate”); *id.* §§ 50-20-704–05, 707 (detail-
 23 ing the in-person, distribution, and informed consent requirements for
 24 abortion-inducing drugs); *id.* § 50-20-711 (“A person who purposely or
 knowingly or negligently violates any provision of this part is guilty of a
 felony[.]”). Even though Montana’s in-person dispensing requirement has

1 been preliminarily enjoined, *Planned Parenthood of Mont. v. State*, 515
 2 P.3d 301, 314-15 (Mont. 2022), Montana intends to enforce that law if
 3 and when the preliminary injunction is dissolved. And the FDA's elimi-
 4 nation of the in-person dispensing requirement will undermine Mon-
 5 tana's ability to enforce its laws and to ensure that mifepristone is ad-
 6 ministered safely and lawfully.

7 74. Montana thus has both quasi-sovereign and sovereign inter-
 8 ests that are harmed by the FDA's decision to eliminate mifepristone's
 9 in-person dispensing requirement.

10 ***The FDA's Action Harms Nebraska and its Residents***

11 75. Nebraska has a sovereign interest in ensuring that its laws
 12 are enforced and not undermined. *See Alfred L. Snapp Son, Inc. v. Puerto*
 13 *Rico ex rel. Pedro Barez*, 458 U.S. 592, 601 (1982). Nebraska law protects
 14 women and prenatal life from abortion-inducing drugs like mifepristone.
 15 *See Neb. Rev. Stat. § 28-335(2).*

16 76. Nebraska thus has both quasi-sovereign and sovereign inter-
 17 ests that are harmed by the FDA's decision to eliminate mifepristone's
 18 in-person dispensing requirement.

19 ***The FDA's Action Harms South Carolina and its Residents***

20 77. South Carolina is principally responsible for ensuring the
 21 safety of its citizens.

22 78. As detailed above, the FDA's decision to eliminate mifepris-
 23 tone's in-person dispensing requirement will harm South Carolina
 24 women and prenatal life.

79. The increased risk to South Carolina women and unborn chil-
 dren will further harm South Carolina by causing it to incur additional

1 medical care expenses, including emergency care, some of which is borne
2 by South Carolina through Medicaid expenditures.

3 80. The longstanding in-person dispensing requirement has also
4 created reliance interests for South Carolina. Effective enforcement of
5 South Carolina law and protection of South Carolina women and unborn
6 children has been built around and depends on mifepristone's REMS—
7 including an in-person dispensing requirement.

8 81. South Carolina thus has both quasi-sovereign and sovereign
9 interests that are harmed by the FDA's decision to eliminate mifepris-
tone's in-person dispensing requirement.

10 ***The FDA's Action Harms Texas and its Residents***

11 82. Texas is principally responsible for ensuring the safety of its
12 citizens.

13 83. As detailed above, the FDA's decision to eliminate mifepris-
14 tone's in-person dispensing requirement will harm Texas women and
15 prenatal life.

16 84. The increased risk to Texas women and unborn children will
17 further harm Texas by causing it to incur additional medical care ex-
18 penses, including emergency care, some of which is borne by Texas
through Medicaid expenditures.

19 85. The longstanding in-person dispensing requirement has also
20 created reliance interests for Texas. Effective enforcement Texas law and
21 protection of Texas women and unborn children has been built around
22 and depends on mifepristone's REMS—including an in-person dispens-
23 ing requirement.
24

1 86. Texas thus has both quasi-sovereign and sovereign interests
2 that are harmed by the FDA's decision to eliminate mifepristone's in-per-
3 son dispensing requirement.

4 ***The FDA's Action Harms Utah and its Residents***

5 87. Utah is principally responsible for ensuring the safety of its
6 citizens.

7 88. As detailed above, the FDA's decision to eliminate mifepris-
8 tone's in-person dispensing requirement will harm Utah women and pre-
9 natal life.

10 89. The increased risk to Utah women and unborn children will
11 further harm Utah by causing it to incur additional medical care ex-
12 penses, including emergency care, some of which is borne by Utah
13 through Medicaid expenditures.

14 90. The longstanding in-person dispensing requirement has also
15 created reliance interests for Utah. Effective enforcement Utah law and
16 protection of Utah women and unborn children has been built around and
17 depends on mifepristone's REMS—including an in-person dispensing re-
18 quirement.

19 91. Utah thus has both quasi-sovereign and sovereign interests
20 that are harmed by the FDA's decision to eliminate mifepristone's in-per-
21 son dispensing requirement.

22 **CLAIM I**
23 **(Violation of 5 U.S.C. § 553 – Notice and Comment Requirement)**

24 92. Plaintiffs reallege and incorporate by reference the facts and
allegations set forth in all preceding paragraphs as if set forth in full
herein.

93. The FDA's promulgation of the mifepristone 2023 REMS was

1 a final agency action that is causing, and will continue to cause, Idaho
2 irreparable harm.

3 94. When the FDA promulgated the mifepristone 2023 REMS, it
4 engaged in rulemaking that was subject to the APA's notice and comment
5 requirements. *See* 5 U.S.C. § 553. No exceptions to the notice and com-
6 ment requirements applied. *See id.*

7 95. The FDA's promulgation of the mifepristone 2023 REMS was
8 done unilaterally and without complying with the notice and comment
9 requirements under the APA.

10 96. Accordingly, the FDA's decision to eliminate mifepristone's in-
11 person dispensing requirement without abiding by the notice and com-
12 ment requirements of the APA is procedurally invalid and must be va-
cated. *See Paulsen v. Daniels*, 413 F.3d 999, 1008 (9th Cir. 2005).

13 **CLAIM II**
14 **(Violation of 5 U.S.C. § 706 – Arbitrary and Capricious Agency**
15 **Action)**

16 97. Plaintiffs reallege and incorporate by reference the facts and
17 allegations set forth in all preceding paragraphs as if set forth in full
18 herein.

19 98. The FDA's promulgation of the mifepristone 2023 REMS was
20 a final agency action that is causing, and will continue to cause, Idaho
21 irreparable harm.

22 99. Mifepristone's in-person dispensing requirement is necessary
23 to assure safe use of the drug.

24 100. The FDA did not adequately explain or support its decision to
eliminate mifepristone's in-person dispensing requirement and it failed

1 to consider relevant and necessary facts and data, including reliance in-
 2 terests. *See Dep't of Homeland Sec. v. Regents of the Univ. of California*,
 3 140 S. Ct. 1891, 1913 (2020); *F.C.C. v. Fox Television Stations, Inc.*, 556
 4 U.S. 502, 513 (2009).

5 101. Moreover, the FDA stated need for eliminating mifepristone's
 6 dispensing requirement was pretextual. *See Dep't of Com. v. New York*,
 7 139 S. Ct. 2551, 2576 (2019).

8 102. Accordingly, the FDA's decision to eliminate mifepristone's in-
 9 person dispensing requirement is "arbitrary, capricious, an abuse of dis-
 10 cretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2)(A).

11 **CLAIM III**
 12 **(Violation of 5 U.S.C. § 706 – Agency Action**
 13 **in Excess of Statutory Authority)**

14 103. Plaintiffs reallege and incorporate by reference the facts and
 15 allegations set forth in all preceding paragraphs as if set forth in full
 16 herein.

17 104. Under the APA, a final agency action is unlawful and must be
 18 set aside if it is "in excess of statutory jurisdiction, authority, or limita-
 19 tions, or short of statutory right." 5 U.S.C. § 706(2)(C).

20 105. The FDCA requires the FDA to impose REMS for dangerous
 21 drugs like mifepristone. 21 U.S.C. § 355-1(a)(1).

22 106. The FDCA specifically includes in-person dispensing as a mit-
 23 igation requirement that the FDA may require. 21 U.S.C. § 355-1(f)(3)(C).

24 107. By eliminating mifepristone's in-person dispensing require-
 ment, the FDA has violated the FDCA's requirement that a REMS must
 "ensure that the benefits of the drug outweigh the risks of the drug," 21
 U.S.C. § 355-1(a)(1), and has thus exceeded its statutory authority. 5

1 U.S.C. § 706(2)(C); *Trout Unlimited v. Pirzadeh*, 1 F.4th 738, 751 (9th
2 Cir. 2021).

3 **PRAYER FOR RELIEF**

4 WHEREFORE, Idaho, Iowa, Montana, Nebraska, South Carolina,
5 Texas, and Utah respectfully request that the Court:

6 (1) Adjudge and declare, pursuant to 28 U.S.C. § 2201, that the
7 FDA's final agency action on January 3, 2023 modifying the mifepristone
8 REMS violated the notice-and-comment requirements under the Admin-
istrative Procedure Act and is therefore invalid;

9 (2) Adjudge and declare, pursuant to 28 U.S.C. § 2201, that the
10 FDA's final agency action on January 3, 2023 modifying the mifepristone
11 REMS is arbitrary, capricious, an abuse of discretion, or otherwise not in
12 accordance with law under the Administrative Procedure Act;

13 (3) Adjudge and declare, pursuant to 28 U.S.C. § 2201, that the
14 FDA's final agency action on January 3, 2023 modifying the mifepristone
15 REMS exceeds the statutory authority granted to the FDA under the
FDCA;

16 (4) Enjoin Defendants, pursuant to 28 U.S.C. § 2202, from enforc-
17 ing or applying the January 3, 2023 mifepristone REMS;

18 (5) Vacate the FDA's January 3, 2023 final agency action;

19 (6) Award Idaho, Iowa, Montana, Nebraska, South Carolina,
20 Texas, and Utah such additional relief as the Court may deem just,
21 proper, and necessary, including their attorneys' fees and costs associ-
22 ated with this litigation.

23 Dated: March 30, 2023
24

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3 DAVID M.S. DEWHIRST
4 Chief Deputy Attorney General

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15 **Application for pro hac vice admis-*
16 *sion forthcoming*

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Exhibit 1



Center for Drug Evaluation and Research

Food and Drug Administration

December 16, 2021

Graham Chelius, M.D.
The Society of Family Planning
The California Academy of Family Physicians

Dear Dr. Chelius:

This letter is to inform you that FDA has completed its review of the Mifepristone Risk Evaluation and Mitigation System (REMS) Program.¹ The agency has determined that the Mifepristone REMS Program continues to be necessary to ensure that the benefits of the drug outweigh the risks. However, we have determined that it must be modified to minimize the burden on the health care delivery system of complying with the REMS and to ensure that the benefits of the drug outweigh the risks. See 21 USC 355-1(g)(4)(B). The modifications to the REMS will consist of: (1) removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals (i.e., the “in-person dispensing requirement”); and (2) adding a requirement that pharmacies that dispense the drug be specially certified.

A REMS Modification Notification letter has been sent to both Applicants subject to the Mifepristone REMS Program. The letter describes the modifications and directs the Applicants to submit prior approval supplements within 120 days. We have also answered a related citizen petition from the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians. That response will be posted in the public docket (Docket No. FDA-2019-P-1534; available at www.regulations.gov).

Sincerely,

Patrizia A.
Cavazzoni -S

Digitally signed by Patrizia A.
Cavazzoni -S
Date: 2021.12.16 15:05:01 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

¹ We also note your letter of September 29, 2021 to us on this subject.

Exhibit 2



Donna J. Harrison, M.D.
Executive Director
American Association of Pro-Life Obstetricians and Gynecologists
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Quentin L. Van Meter, M.D., FCP
President
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P.O. Box 357190
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December 16, 2021

Re: Docket No. FDA-2019-P-1534

Dear Drs. Harrison and Van Meter:

This letter responds to your citizen petition submitted to the Food and Drug Administration (FDA or Agency) on March 29, 2019, on behalf of the American Association of Pro-Life Obstetricians and Gynecologists and the American College of Pediatricians (Petition). In the Petition, you request that FDA: (1) restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, and (2) retain the Mifeprex Risk Evaluation and Mitigation Strategy (REMS) and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

Specifically, in your Petition you request that the Agency:

- (1) Restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000, to include the following:
 - Indications and Usage - Mifeprex, in a regimen with misoprostol, for the termination of intrauterine pregnancy, should be limited to 49 days gestation.
 - Dosage and Administration:
 - Mifeprex should be administered by or under the supervision of a physically present and certified physician who has ruled out ectopic pregnancy.
 - The use of Mifeprex and misoprostol for the termination of pregnancy should require three office visits by the patient.

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- Contraindications - Mifeprex use is contraindicated for patients who do not have convenient access to emergency medical care.
- Adverse Event Reporting - Certified prescribers, emergency medical personnel, physicians treating complications, and Danco Laboratories should report to FDA's MedWatch Reporting system any deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications following the use of Mifeprex and misoprostol.
- Additional studies - The Mifeprex REMS should require a formal study of outcomes for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients who have limited access to emergency room services; and patients who self-administer misoprostol.

(2) Retain the Mifeprex REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.

We have carefully considered the information submitted in your Petition and other relevant data available to the Agency. Based on our review of this information, your Petition is granted in part and denied in part.

I. BACKGROUND

A. Mifeprex

On September 28, 2000, FDA approved Mifeprex for the medical termination of intrauterine pregnancy through 49 days' pregnancy (new drug application (NDA) 020687). The application was approved under part 314, subpart H (21 CFR part 314, subpart H), "Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses" (subpart H). Specifically, § 314.520 of subpart H provides for approval with restrictions that are needed to assure the safe use of the drug product. In accordance with § 314.520, FDA restricted the distribution of Mifeprex as specified in the September 2000 approval letter.¹

Subsequently, Mifeprex was identified as one of the products that was deemed to have in effect an approved REMS under the Food and Drug Administration Amendments Act of 2007 (FDAAA) because on the effective date of Title IX, subtitle A of FDAAA (March 28, 2008), Mifeprex had in effect elements to assure safe use.² Accordingly, in June 2011, we approved a REMS for Mifeprex, consisting of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS.

Elements to assure safe use included: (1) prescriber certification (ETASU A); (2) that Mifeprex is dispensed only in certain healthcare settings by or under the supervision of a certified prescriber

¹ See https://www.accessdata.fda.gov/drugsatfda_docs/appltr/2000/20687appltr.pdf.

² 73 FR 16313 (Mar. 27, 2008).

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(ETASU C); and (3) that Mifeprex is dispensed only with documentation of safe use conditions (ETASU D). Documentation of safe use conditions consists of a Patient Agreement Form between the prescriber and the patient indicating that the patient has received counseling from the prescriber regarding the risk of serious complications associated with Mifeprex.

On March 29, 2016, we approved an efficacy supplement (S-020) to NDA 020687 for Mifeprex submitted by the applicant Danco Laboratories, LLC (S-020 efficacy supplement). The approval included changes in the dose of Mifeprex and the dosing regimen for taking Mifeprex and misoprostol (including the dose of misoprostol and a change in the route of misoprostol administration from oral to buccal (in the cheek pouch); the interval between taking Mifeprex and misoprostol; and the location at which the patient may take misoprostol). The approval also modified the gestational age up to which Mifeprex has been shown to be safe and effective, as well as the process for follow-up after administration of the drug.

Specifically, the following changes, among others, were made as part of the 2016 approval:³

- Revised the dosing regimen to consist of 200 mg of Mifeprex taken by mouth, followed in 24-48 hours by 800 mcg of misoprostol taken buccally (in the cheek pouch). This differs from the originally approved dosing regimen of 600 mg of oral Mifeprex followed 48 hours later by 400 mcg of oral misoprostol.
- Revised the indication for use of Mifeprex, in a regimen with misoprostol, to extend the maximum gestational age for the medical termination of intrauterine pregnancy from 49 days to 70 days.
- Reduced the number of office visits by the patient under the approved regimen from three to one.
- Replaced the term “physician” with the term “healthcare provider.”

In addition, after reviewing the data and information submitted by the applicant in the S-020 efficacy supplement, and after taking into consideration the safety data that had become available since the initial approval of Mifeprex in 2000, we determined the Mifeprex REMS continued to be necessary to ensure the benefits of the product outweigh the risks. However, we approved modifications to the Mifeprex REMS that reflected the changes approved in the efficacy supplement. These changes to the REMS included, among others:⁴

- Updating the Prescriber Agreement Form to reflect the revised indication and dosing regimen.
- Removing the Medication Guide as a REMS element (but retaining the Medication Guide as labeling).

³ See https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2016/020687Orig1s020ltr.pdf and https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf.

⁴ See https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020RemsR.pdf.

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- Removing the requirement that certified prescribers report certain enumerated adverse events to the applicant (specifically, any hospitalization, transfusion or other serious adverse events), but retaining the requirement that certified prescribers report all deaths to the sponsor.

Under the March 2016 approval, the Mifeprex REMS also continued to require that Mifeprex be dispensed to patients only in certain healthcare settings, specifically, clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber.⁵

B. Generic Version of Mifeprex

On April 11, 2019, we approved GenBioPro, Inc.'s generic version of Mifeprex, Mifepristone Tablets, 200 mg (abbreviated new drug application (ANDA) 091178). This action took place after this Petition was submitted to the Agency. As required by 21 CFR 314.94(a)(8), GenBioPro's approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, has the same labeling (with certain permissible differences) as the brand product it references, Mifeprex. Accordingly, although we refer to the Mifeprex labeling in several sections of this response, our discussions in this response apply equally to both the NDA and the generic product labeling, unless otherwise specifically noted.⁶

GenBioPro's generic version of Mifeprex is subject to the same ETASU as its listed drug (21 U.S.C. -1(i)). At the time we approved GenBioPro's generic version of Mifeprex, that ANDA product was required to use a single, shared system for the ETASU with the brand drug product, Mifeprex, unless the requirement was waived by FDA (21 U.S.C. 355-1(i)). FDA did not waive this requirement. Accordingly, at the same time that FDA approved GenBioPro's generic version of Mifeprex in 2019, FDA approved a supplemental new drug application (sNDA) for Mifeprex, approving modifications to the existing, approved REMS for Mifeprex to establish a single, shared system REMS for mifepristone products for the medical termination of intrauterine pregnancy through 70 days gestation (referred to as the Mifepristone REMS Program). In establishing the single, shared system REMS in 2019, no substantive changes were made to the ETASU in the March 2016 Mifeprex REMS. References to the REMS in this response refer to the Mifepristone REMS Program established in 2019, unless otherwise noted.

C. In-Person Dispensing Requirement During the COVID-19 PHE

⁵ See https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/020687Orig1s020ltr.pdf.

⁶ We note that Korlym and the generic version of Korlym (Mifepristone Tablets, 300 mg) contain the same active ingredient – mifepristone – as Mifeprex and the generic version of Mifeprex (Mifepristone Tablets, 200 mg). Although these drug products contain the same active ingredient, their intended uses target different receptors, and the products have different strengths and use different dosing regimens. Korlym and the generic version of Korlym are approved for the control of hyperglycemia (high blood sugar levels) due to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes or glucose intolerance, and have failed surgery or are not candidates for surgery. References to mifepristone in this response refer to the use of mifepristone for the medical termination of intrauterine pregnancy through 70 days gestation, unless otherwise noted.

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FDA has recognized that during the COVID-19⁷ public health emergency (PHE),⁸ certain REMS requirements for various products may be difficult to comply with because patients may need to avoid public places and patients suspected of having COVID-19 may be self-isolating and/or subject to quarantine. The Agency has also received queries concerning products with REMS that have ETASUs, including REMS with ETASUs that restrict distribution, and the impact of such ETASUs on patient access when patients self-isolate or are subject to quarantine.

In April 2021, FDA communicated its intent to exercise enforcement discretion during the COVID-19 PHE regarding the requirement in the Mifepristone REMS Program that mifepristone used for medical termination of intrauterine pregnancy through 70 days gestation be dispensed to patients by or under the supervision of a certified prescriber only in certain healthcare settings, specifically clinics, medical offices, and hospitals (referred to as the “in-person dispensing requirement”).

Specifically, FDA communicated that provided all other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion with respect to the in-person dispensing requirement of the Mifepristone REMS Program, including any in-person requirements that may be related to the Patient Agreement Form, during the COVID-19 PHE. This determination, which FDA made on April 12, 2021, was effective immediately. We also note that from July 13, 2020 to January 12, 2021, per a court order, FDA was enjoined from enforcing the in-person dispensing requirement of the Mifepristone REMS Program.⁹

Further, and as we also communicated on April 12, 2021, to the extent all of the other requirements of the Mifepristone REMS Program are met, the Agency intends to exercise enforcement discretion during the COVID-19 PHE with respect to the dispensing of Mifeprex or the approved generic version of Mifeprex, Mifepristone Tablets, 200 mg, through the mail, either by or under the supervision of a certified prescriber, or through a mail-order pharmacy when such dispensing is done under the supervision of a certified prescriber.

FDA’s intent to exercise enforcement discretion with respect to these requirements during the COVID-19 PHE was the result of a thorough scientific review by experts within FDA’s Center for Drug Evaluation and Research (CDER), who evaluated relevant information, including available clinical outcomes data and adverse event reports.

D. Minor Modification

⁷ The virus has been named “SARS-CoV-2” and the disease it causes has been named “Coronavirus Disease 2019” (COVID-19).

⁸ Secretary of Health and Human Services, Determination that a Public Health Emergency Exists (originally issued Jan. 31, 2020, and subsequently renewed), *available at* <https://www.phe.gov/emergency/news/healthactions/phe/Pages/default.aspx>.

⁹ *Am. Coll. of Obstetricians & Gynecologists v. FDA*, 472 F. Supp. 3d 183, 233 (D. Md. July 13, 2020), order clarified, 2020 WL 8167535 (D. Md. Aug. 19, 2020) (preliminarily enjoining FDA from enforcing the in-person dispensing requirement and any other in-person requirements of the Mifepristone SSS REMS); *FDA v. Am. Coll. of Obstetricians & Gynecologists*, 141 S. Ct. 578 (Jan. 12, 2021) (staying the preliminary injunction imposed by the District Court).

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In response to a request submitted by the applicants, FDA approved a minor modification to the Mifepristone REMS Program on May 14, 2021. This minor modification revised the Patient Agreement Form to use gender neutral language. Specifically, the pronouns “she” and “her” in the Patient Agreement Form were replaced with “the patient.” The minor modification also included revisions to the REMS document to be consistent with the revisions to the Patient Agreement Form. These changes did not affect the substance of the Patient Agreement Form, the REMS document, or the Mifepristone REMS Program.

E. Review of the Mifepristone REMS Program

In 2021, FDA also undertook a full review of the Mifepristone REMS Program.¹⁰ In conducting this review, FDA reviewed multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FDA Adverse Event Reporting System (FAERS) reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation, as well as information submitted by the sponsors of the NDA and the ANDA (together, the Applicants). As discussed in more detail below, based on our review of this information, FDA has determined that certain elements of the Mifepristone REMS Program remain necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation; and therefore, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risk. Specifically, we find that the healthcare provider certification and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions continue to be necessary components of the REMS to ensure the benefits of mifepristone outweigh the risks for this indication.

We also find that the in-person dispensing requirement is no longer necessary to assure the safe use of mifepristone for medical termination of intrauterine pregnancy through 70 days gestation. We have concluded that mifepristone will remain safe and effective for medical abortion if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added.¹¹ Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Accordingly, today we are sending a REMS Modification Notification letter to both Applicants in the Mifepristone REMS Program. As stated in that letter, FDA has concluded that a modification is necessary and must include the following changes:

- Removing the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

¹⁰ We note that the Agency is in litigation regarding the Mifepristone REMS Program and committed to conducting a full review of the Mifepristone REMS Program, including reviewing any relevant data and evidence submitted to the Agency by the Plaintiffs in that litigation (*Chelius et al v. Becerra*, Joint Mot. to Stay Case Pending Agency Review, ECF No. 148, May 7, 2021, Civ. No. 1:17-00493 (D. Haw.)).

¹¹ Although we have determined that the Mifepristone REMS Program must be modified to add a requirement for pharmacy certification, this was not raised in your Petition and therefore is not discussed further in this response.

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- Adding a requirement that pharmacies that dispense the drug be specially certified.

II. DISCUSSION OF ISSUES RAISED

A. Mifeprax Regimen

1. Indications and Usage

In the Petition, you ask FDA to restore and strengthen elements of the Mifeprax regimen and prescriber requirements approved in 2000, to limit Mifeprax, in a regimen with misoprostol, for the termination of intrauterine pregnancy, to 49 days gestation (Petition at 1 and 3). For the reasons explained below, we deny this request.

Citing to a 2011 study and a practice bulletin issued by the American College of Obstetricians and Gynecologists (ACOG), you state that medical abortion¹² regimens demonstrate an increase in complications and failures, including serious risks of hemorrhage, infection, and ongoing pregnancy, after 49 days gestation (Petition at 3-4).

Our review of the S-020 efficacy supplement in 2016 concluded that Mifeprax, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.¹³ Complete medical abortion rates from the pivotal clinical trials relied on for the initial approval of Mifeprax (with an indication for medical termination of intrauterine pregnancy through 49 days gestation) were 92.1 percent and 95.5 percent in the United States and French trials, respectively.¹⁴ The studies reviewed in support of the 2016 approval for Mifeprax (with an indication for medical termination of intrauterine pregnancy through 70 days gestation) showed comparable efficacy. The 2016 Clinical Review of the S-020 efficacy supplement summarized clinical outcomes and adverse effects from 22 studies (7 in the United States and 15 from outside the United States) through 70 days gestation, using the currently approved regimen of 200 mg oral mifepristone with 800 mcg buccal misoprostol. The ranges of complete medical abortion rates calculated by the clinical reviewer were 93.2 percent to 98.7 percent in the United States studies, and 92 percent to 98 percent in the non-United States studies.¹⁵

Serious adverse events associated with the use of mifepristone through 70 days gestational age are rare. Per the current mifepristone labeling, the rates of serious adverse events are low: transfusions are 0-0.1 percent, sepsis is less than 0.01 percent, hospitalization related to medical abortion is 0-0.7 percent, and hemorrhage is 0.1 percent.¹⁶ As discussed

¹² In this response, the terms “medical abortion” and “medication abortion” both refer to the use of mifepristone, in a regimen with misoprostol, for the medical termination of intrauterine pregnancy.

¹³ See 2016 Clinical Review available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020MedR.pdf, at 32-38 and 47-47.

¹⁴ See 1999 Medical Officer’s Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/20687_Mifepristone_medr_P1.pdf, at 11 (Table 1) and 16.

¹⁵ See 2016 Clinical Review, *supra* n. 13, at 28-31.

¹⁶ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

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throughout this response, the benefit/risk assessment supported our 2016 conclusion that the product is safe and effective through 70 days gestation.

In support of your assertion that medical abortion demonstrates an increase in complications after 49 days gestation, you cite to Mentula, et al.,¹⁷ a register-based, retrospective cohort study that included 18,248 women in Finland who underwent medical abortion between January 1, 2003, and December 31, 2006 (Petition at 3). As an initial matter, we note that the Mentula study was primarily designed to assess the immediate adverse events following medical abortion in the second trimester (13 to 24 gestational weeks as defined by the authors) and then compare those events to those identified with medical abortion in the first trimester (up to 12 gestational weeks as defined by the authors). The study was not designed to compare rates of complications across gestational weeks within the first trimester. It is true that the Mentula publication includes information on the percentages of women who had surgical evacuation following medical abortion and the percentages of women who had infection following medical abortion, based on weekly gestational age, from 5 weeks to 20 weeks gestation.¹⁸ However, the data in the Mentula study are relatively old (2003-2006); in our 2016 review of the S-020 efficacy supplement, we conducted an extensive review of more recent data¹⁹ and concluded that Mifeprex, in a regimen with misoprostol, is safe and effective for medical termination of intrauterine pregnancy through 70 days gestation.

You also cite to ACOG Practice Bulletin No. 143, which states: “the risk of clinically significant bleeding and transfusion may be lower in women who undergo medical abortion of gestations up to 49 days compared with those who undergo medical abortion of gestations of more than 49 days.”²⁰ This statement is based on a 1998 publication which evaluated patients undergoing medical abortion with mifepristone 600 mg and then oral misoprostol 400 mcg two days later.²¹ The regimen studied in this 1998 publication is not the currently approved regimen for mifepristone in the United States. Further, ACOG Practice Bulletin No. 143 has been withdrawn and replaced by Practice Bulletin No. 225, which was published in October 2020 and no longer contains this statement.²²

You also state that the failure rate of the approved regimen (which you refer to as the “buccal misoprostol regimen”) increases as the gestational age increases, especially at

¹⁷ Mentula MJ, Niinimäke M, Suhonen S, et al. Immediate Adverse Events After Second Trimester Medical Termination of Pregnancy: Results of a nationwide registry study, *Human Reproduction*. 2011;26(4):927-932.

¹⁸ *Id.* at Fig. 2 and Fig. 3. Surgical intervention after medical abortion and infection after medical abortion are two distinct adverse events. The calculation of abortion completion rates accounts for the need for surgical intervention. In clinical studies we reviewed, success of medical abortion was defined as the complete expulsion of the products of conception without the need for surgical intervention.

¹⁹ See 2016 Cross-Discipline Team Leader Review, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/020687Orig1s020CrossR.pdf, at 37 (Table 4).

²⁰ Petition at 3. See Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); *Obstet Gynecol*. 2014 Mar;123(3):676-692 at 680.

²¹ Spitz I, Bardin CW, Benton L, Robbins A. Early pregnancy termination with mifepristone and misoprostol in the United States, *NEJM*. 1998;338 (18):1241-1247.

²² See ACOG Practice Bulletin No. 225. Medication Abortion Up to 70 Days of Gestation. *Obstetrics and Gynecology* 2020; 136(4); e31 to e47.

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gestational ages greater than 49 days, relying on a 2015 meta-analysis,²³ and that the gestational limit should not have been increased (Petition at 3-4). We agree that the failure rate of medical abortion regimens, including the currently approved regimen, generally increases with increasing gestational age. However, the increase in failure rate with each incremental week of gestation, as described in approved mifepristone labeling and in this 2015 meta-analysis, is small, and we believe that the benefit/risk profile for medical termination of intrauterine pregnancy between 49 and 70 days gestation remains acceptable.

For these reasons, we deny your request that FDA limit mifepristone, in a regimen with misoprostol for the termination of intrauterine pregnancy, to 49 days gestation.

2. Dosage and Administration

a. Prescriber Qualifications

You state that FDA should limit the “ability” to prescribe and dispense Mifeprex to qualified, licensed physicians, rather than permitting non-physicians to apply to be certified prescribers, because of the regimen’s serious risks and because physicians are better trained to diagnose patients who have contraindications to Mifeprex and to verify gestational age (Petition at 4). We do not agree.

Healthcare providers who are licensed to prescribe can become certified in REMS programs if they are able to meet the applicable REMS requirements. To become certified to prescribe mifepristone under the Mifepristone REMS Program, the prescriber must review the prescribing information for mifepristone and complete a Prescriber Agreement Form. By signing the form, the prescriber agrees that they meet certain qualifications, including the ability to date pregnancies accurately and to diagnose ectopic pregnancies. These healthcare providers must also: (1) be able to provide any necessary surgical intervention or have made arrangements for others to provide for such care; or (2) be able to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.²⁴

In our review of the S-020 efficacy supplement in 2016, we determined that available data support that Mifeprex is safe and effective when prescribed by midlevel providers, such as physician assistants and nurse practitioners, as well as by physicians.²⁵ Our 2016 review included four studies that evaluated the safety and efficacy of medical abortion when performed by non-physician healthcare providers. Two trials evaluated the currently

²³ Petition at 4, fn. 6 (citing Chen MJ, Creinin MD, *Mifepristone with Buccal Misoprostol for Medical Abortion*, *Obstet. Gynecol* 126 (1) July 2015 12-21).

²⁴ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s0221b1.pdf; see also <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=390>.

²⁵ See 2016 Clinical Review, *supra* n. 13, at 79; see also 2016 Cross-Discipline Team Leader Review, *supra* n. 19, at 17-18. We also note that in most states, midlevel clinicians, such as physician assistants and nurse practitioners, are licensed to prescribe medications.

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approved Mifeprex and buccal misoprostol regimen (Olavarrieta and Kopp Kallner);^{26,27} one trial studied a regimen using vaginal misoprostol (Warringer);²⁸ a fourth study did not specify the route of misoprostol administered (Puri).²⁹ Olavarrieta reported a completion rate of 97.9 percent when medical abortion was provided by nurses as compared with 98.4 percent with physicians. Kopp Kallner reported a completion rate of 99 percent with certified nurse midwives versus 97.4 percent with physicians. Warringer reported an abortion completion rate of 97.4 percent with nurses as compared with 96.3 percent with physicians. Puri reported an abortion completion rate of 96.8 percent when the service was provided by nurse-midwives as compared with 97.4 percent in the “standard care” group.³⁰ Our 2016 review also included a systematic review of six controlled clinical studies by Renner;³¹ the authors concluded that the evidence “indicates that trained mid-level providers may effectively and safely provide first trimester surgical and medical termination of pregnancy services.” Additionally, Barnard et al., in a Cochrane systematic review, assessed the safety and effectiveness of abortion procedures administered by mid-level providers (nurse practitioners, midwives, other non-physician healthcare providers) compared to doctors.³² The authors concluded, based in part on two of the studies that we had reviewed in 2016,³³ that there was no statistically significant difference in the risk of failure for medical abortions performed by mid-level providers compared with doctors.

We also believe that the identification of patients for whom the use of mifepristone is contraindicated can be done by mid-level healthcare providers, as well as physicians. Mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation is contraindicated in patients with any of the following conditions:³⁴

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass

²⁶ Olavarrieta CD, Ganatra B, Sorhaindo A, et al. Nurse versus Physician-provision of Early Medical Abortion in Mexico: A Randomized Controlled Non-Inferiority Trial. *Bull World Health Organ.* 2015;93:249-258.

²⁷ Kopp Kallner H, Gomperts R, Salomonsson E, et al. The efficacy, safety and acceptability of medical termination of pregnancy provided by standard care by doctors or by nurse-midwives: a randomised controlled equivalence trial. *BJOG.* 2015; 122: 510-517.

²⁸ Warriner IK, Wang D, et al. Can midlevel health-care providers administer early medical abortion as safely and effectively as doctors? A randomized controlled equivalence trial in Nepal. *Lancet.* 2011; 377: 1155-61.

²⁹ Puri M, Tamang A, Shrestha P, et al. The role of auxiliary nurse-midwives and community health volunteers in expanding access to medical abortion in rural Nepal. *Reproductive Health Matters.* 2015; 22(44) 94-103.

³⁰ 2016 Clinical Review, supra n. 13, at 43.

³¹ Renner RM, Brahmi D, Kapp N. Who can provide effective and safe termination of pregnancy care? A systematic review. *BJOG* 2013 Jan;120(1):23-31.

³² Barnard S, Kim C, Park MN, Ngo TD. Doctors or mid-level providers for abortion (Review). *Cochran Database of Systematic Reviews.* 2015, Issue 7.

³³ Of the medical abortion studies reviewed by Barnard et al (Id.), two were reviewed by the Agency as part of the review of the S-020 supplement in 2016. See Warriner et al (supra n. 28) and Kopp Kallner et al (supra n. 27). The third used a different dose of misoprostol than the currently approved regimen. See Jejeebhoy SJ, Kalyanwalaa S, Zaviera AJF, Kumara R, Mundle S, Tankc J, et al. Feasibility of expanding the medication abortion provider based in India to include ayurvedic physicians and nurses. *International Perspectives on Sexual and Reproductive Health* 2012;38(3)133-42)

³⁴ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

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- An intrauterine device in place
- Chronic adrenal failure
- Concurrent long-term corticosteroid therapy
- History of allergy to mifepristone, misoprostol, or other prostaglandins
- Hemorrhagic disorder or concurrent anticoagulant therapy
- Inherited porphyrias

These contraindications can be assessed by trained healthcare providers who prescribe mifepristone by obtaining a medical history, from medical records, and/or from physical examination or ultrasound if appropriate. We continue to believe that available data support the conclusion that mid-level healthcare providers, as well as physicians, possess the clinical and counseling skills necessary to provide medical abortion. We note this is consistent with ACOG's statement in its current practice bulletin that "[i]n addition to physicians, advanced practice clinicians, such as nurse-midwives, physician assistants, and nurse practitioners, possess the clinical and counseling skills necessary to provide first-trimester medical abortion."³⁵ Further, if necessary, ultrasound training and certification is available to nurse practitioners and physician assistants, as well as physicians.³⁶ In sum, available information supports that mid-level healthcare providers as well as physicians can determine whether mifepristone is an appropriate treatment for a particular patient and dispense it.

You also assert that FDA should strengthen the requirement that providers accurately assess the duration of the pregnancy by mandating that gestational age be assessed by ultrasound (Petition at 5). We refer you to FDA's 2016 Response to the citizen petition submitted to Docket No. FDA-2002-P-0364 (the "2016 CP Response"), where FDA stated that the determination of gestational age does not always require an ultrasound. In the 2016 CP Response, FDA stated it had "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy. These decisions should be left to the professional judgment of each provider, as no method (including TVS [transvaginal ultrasound]) provides complete accuracy. The approved labeling for Mifeprex recommended ultrasound evaluation as needed, leaving this decision to the judgment of the provider."³⁷

In the Petition, you reference the Prescriber Agreement Form, in which the provider must attest they have the ability to: (1) accurately assess the duration of the pregnancy; (2) diagnose ectopic pregnancies; and (3) provide surgical intervention if needed (or have made plans to provide such care through others), and you state that a provider who does not physically meet with and examine a patient, but simply consults with the patient over the Internet, is not capable of fulfilling these requirements, or of ruling out additional

³⁵ ACOG Practice Bulletin No. 225, *supra* n. 22.

³⁶ American Institute of Ultrasound in Medicine. Accessed November 26, 2021. <https://www.aium.org/officialStatements/70>.

³⁷ FDA's citizen petition response dated March 29, 2016, to the citizen petition submitted by the American Association of Pro-Life Obstetricians and Gynecologists, the Christian Medical and Dental Association, and Concerned Women for America on August 20, 2002, Docket No. FDA-2002-P-0364 at 18. See <https://www.regulations.gov/document/FDA-2002-P-0364-0002>.

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contraindications (Petition at 5-6). You state that FDA should require certified prescribers to be physically present when Mifeprex is dispensed so that they can appropriately examine patients and rule out contraindications to the use of Mifeprex (Petition at 4).

Certified prescribers do not have to be physically present with the patient as long as they have confirmed the patient's gestational age and intrauterine pregnancy. As noted above, in the 2016 CP response, FDA "determined that it was inappropriate for us to mandate how providers clinically assess women for duration of pregnancy and for ectopic pregnancy."³⁸ Moreover, the evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber and can be done in different types of healthcare settings. A certified prescriber can also review the Patient Agreement Form³⁹ with the patient, fully explain the risks of the mifepristone treatment regimen, and answer any questions, as in any consent process, without physical proximity. See also section II.B.1.c (ETASU C – In-person Dispensing).

With respect to providing surgical intervention in cases of incomplete abortion or severe bleeding and assuring patient access to medical facilities equipped to provide blood transfusions and resuscitation (if necessary), the Prescriber Agreement Form does not reflect a requirement that the certified prescriber must provide such care personally; rather, the prescriber must agree that they have the ability to provide such care or that they have made plans to provide such care through others, and that they have the ability to assure the patient has access to appropriate medical facilities. It is common practice for healthcare providers to provide emergency care coverage for other healthcare providers' patients, and in many places, hospitals employ "hospitalists" to provide care to all hospitalized patients. We also note ACOG's statement that "[i]n rare cases, a patient who undergoes a medication abortion may need to obtain an additional intervention, such as uterine aspiration. If the prescribing clinician does not perform the intervention, it is medically appropriate to provide a referral."⁴⁰

For these reasons, we deny your request that FDA limit the "ability" to prescribe and dispense mifepristone to licensed physicians, and we deny your request that FDA require certified providers to physically meet with and examine the patient.

b. Office Visits and Administration of Mifepristone/Misoprostol

In the Petition, you state that the use of mifepristone and misoprostol should require three office visits by the patient (Petition at 7). In support of this position, you state the following:

- Drug-induced abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 10).

³⁸ Id.

³⁹ See <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=390>.

⁴⁰ ACOG Practice Bulletin Number 225 supra n. 22.

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- Abortion complications are more frequent when women abort at home and more healthcare oversight is needed (Petition at 8).
- Home administration of misoprostol does not permit healthcare providers to control when their patients take misoprostol and without monitoring:
 - a patient may take buccal misoprostol before the minimum 24-hour period after taking Mifeprex, which leads to a significantly increased failure rate (Petition at 7).
 - a patient may swallow misoprostol rather than administer it buccally, and oral administration is not as effective as buccal administration in ending the pregnancy (Petition at 7).
- Because providers may now “confirm” that a patient’s drug-induced abortion was successful without a clinic visit, this increases the threat that Rh-negative patients will not receive Rhogam, which is necessary to prevent serious risks in subsequent pregnancies (Petition at 7 and 9).

We address each of these points below.

i. Follow-up Care

The safe use of mifepristone when used in the approved regimen with misoprostol is not contingent on a specific number of office visits being made by the patient undergoing a medical termination of pregnancy. The 2016 labeling change for Mifeprex regarding post-treatment assessment, including the change to the approved regimen to reduce the number of offices visits from three to one, was based on evidence reviewed in the S-020 efficacy supplement. We concluded, upon reviewing the data, that three office visits were not necessary to assure the safe use of Mifeprex.⁴¹

In your Petition, you point to statements by ACOG that medical abortion is contraindicated for patients who are not available for follow-up contact or evaluation (Petition at 8, 10). The ACOG statements you point to are from ACOG Practice Bulletin No. 143, which has been withdrawn and replaced by Practice Bulletin No. 225.⁴² Neither of the statements from the withdrawn Practice Bulletin nor Practice Bulletin No. 225 contraindicate medical abortion in women who are not available for an in-clinic follow-up visit. The current ACOG recommendations indicate that for medical abortion, “[f]ollow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility.”⁴³ The patient and their healthcare provider should determine the best option for follow-up as part of the consultation and consent process.⁴⁴ As reflected in ACOG’s guidance, appropriate follow-

⁴¹ See 2016 Clinical Review, *supra* n. 13, at 44 and 64-67.

⁴² ACOG Practice Bulletin Number 225, *supra* n. 22.

⁴³ *Id.*

⁴⁴ *Id.*

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up after medical termination of a pregnancy may be accomplished in multiple ways and not all require an in-clinic visit.

You also question findings in multiple studies that evaluated the effectiveness of semiquantitative urine pregnancy tests (multi-level pregnancy tests, or MLPT) and low sensitivity urine pregnancy tests (LSPT) to rule out on-going pregnancies and assessed the ability of patients to self-administer these tests and interpret the test results (Petition at 9-10). Overall, these studies concluded that in the majority of women, it is feasible to use a simplified test to determine if further follow-up is necessary. A recent systematic review and meta-analysis by Baiju assessed the effectiveness and safety of self-assessment of the outcome of medical abortion completed at home versus routine clinic follow-up after medical abortion, concluding self-assessment was not inferior to routine clinic follow-up.⁴⁵ We note that this is consistent with current ACOG recommendations, which state that “follow-up can be performed by telephone at 1 week, with subsequent at-home urine pregnancy testing at 4 weeks after treatment, which avoids the need for the patient to go to a facility.”⁴⁶

You also assert that it is important for a patient to be under observation after taking misoprostol to ensure that they are appropriately monitored and provided sufficient pain medication (Petition at 8). You cite the World Health Organization (WHO)’s statement in guidance that up to 90 percent of women will abort within 4-6 hours after taking misoprostol; you further state that the 2000 regimen permitted patients to be in the clinic during this time period (Petition at 8). Your reference to the WHO guidance document⁴⁷ appears to be out of context. The WHO guidance takes no position on whether women should return to and remain in the clinic during a follow-up visit for purposes of taking misoprostol; in fact, it explicitly recognizes that post-abortion care may not require a follow-up visit if the patient is adequately counseled.⁴⁸ In the United States, and as reflected in the approved labeling, medical termination of pregnancy usually involves patients terminating the pregnancy at home, with appropriate follow-up that may not include a return visit.

ii. At Home Medical Abortion and Healthcare Oversight

In addition, you cite a 2018 study to support your statement that abortion complications are more frequent when women abort at home (Petition at 8). The study evaluated complications following medical abortion (both less than 12 weeks and more than 12 weeks gestation) as well as following surgical abortion, at one hospital in Sweden between 2008 and 2015.⁴⁹ For the years 2008 to 2010, data were collected retrospectively; for the years

⁴⁵ Baiju, N, Acharya, G, D’Antonio, F, et al. 2019. Effectiveness, safety and acceptability of self-assessment of the outcome of first-trimester medical abortion: a systematic review and meta-analysis. *BJOG*; 126:1536-1544.

⁴⁶ ACOG Practice Bulletin Number 225, *supra* n. 22.

⁴⁷ World Health Organization, *Safe Abortion: technical and policy guidance for health systems* – 2nd edition. 2012. Page 45 and Section 2.2.2.1 Medication for pain.

⁴⁸ *Id.* at Section 2.3 Post-abortion care and follow-up, at 52.

⁴⁹ Carlsson I, Breiding K, Larsson PG, 2018, Complications Related to Induced Abortion: A Combined Retrospective and Longitudinal Follow-up Study, *BMC Women’s Health* 18:158.

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2011 to 2015, data were collected prospectively. In this study, medical abortions after 12 gestational weeks all occurred at the hospital. The authors report that, among medical abortions less than 12 weeks, the complication frequency increased from 5.4 percent (2008 to 2010) to 8.2 percent (2015). However, the authors also compared the complications related to medical abortions that occurred at less than 12 gestational weeks between “at home” abortions (managed as an outpatient) and “at the hospital” abortions, in 2015 and found no statistically significant difference (8.2 percent “at home” versus 8.0 percent at the hospital). For pregnancies less than or equal to 9 gestational weeks, the rates are similar for the “at home” group (10.0 percent) and the “at the hospital” group (9.3 percent). Notably, as part of our review and approval of the S-020 efficacy supplement in 2016, we assessed serious adverse events by gestational age, including hospitalizations, serious infection requiring hospitalization or intravenous antibiotics, bleeding requiring transfusion, and ectopic pregnancy, as reported in the literature submitted by the Applicant. We concluded that these serious adverse events are rarely reported in the literature and that the regimen of mifepristone 200 mg followed by buccal misoprostol 800 mcg in 24-48 hours is safe to approve for use through 70 days gestation.⁵⁰

You also state that medical abortion is a longer process than surgical abortion and that it requires more attention and care from healthcare providers (Petition at 10). We agree that medical abortion can be a longer process than surgical abortion,⁵¹ but we disagree that medical abortion always requires in-person follow-up with a healthcare provider. Not all of the complications associated with medical abortion necessarily require more intensive management from healthcare providers during a follow-up visit. The question of whether to include an in-person follow-up visit should be discussed by the healthcare provider and the patient. We have concluded that medical abortions are safe and effective for patients who are appropriate candidates and reducing the number of clinic visits does not compromise patient safety.

The current approved labeling for mifepristone for medical termination of pregnancy states that complete pregnancy termination “can be confirmed by medical history, clinical examination, human Chorionic Gonadotropin (hCG) testing, or ultrasonographic scan.” Not all these modalities require an in-clinic assessment during a follow-up visit. Our review of the S-020 efficacy supplement concluded that “available data support ... that there are a variety of follow-up modalities that can adequately identify the need for additional intervention.”⁵² We note that these findings are also consistent with ACOG guidelines, which state that “[r]outine in-person follow-up is not necessary after uncomplicated medication abortion” and recommend several methods for post-treatment follow-up, as appropriate, including serial serum hCG testing alone or telephone follow-up at one week after treatment followed by urine pregnancy testing at four weeks after treatment.⁵³ Because there is more than one effective method to detect an on-going pregnancy, we conclude that the way in which post-treatment follow-up is performed may be determined by the healthcare provider and the patient.

⁵⁰ 2016 Clinical Review, supra n. 13, at 51-57.

⁵¹ See ACOG Practice Bulletin Number 225, supra note 22.

⁵² 2016 Cross Discipline Team Leader Review, supra n. 19, at 17.

⁵³ ACOG Practice Bulletin Number 225, supra note 22.

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iii. Misoprostol

In the Petition, you make a number of assertions regarding the use of misoprostol. We address each in turn.

First, you assert that a patient may take misoprostol before the prescribed minimum 24-hour period after taking Mifeprex, thereby rendering the regimen ineffective, and that home administration of misoprostol does not permit health providers to control when their patients take misoprostol (Petition at 7). You similarly assert that the use of buccal misoprostol sooner than 24 hours after administering mifepristone leads to significantly increased failure rates (Petition at 7).

As an initial matter, our review of the S-020 efficacy supplement in 2016 included data that evaluated the home use of misoprostol in over 30,000 women. The data showed that Mifeprex was safe and effective in a regimen with misoprostol when misoprostol was self-administered at home.⁵⁴ Therefore, any incorrect administration resulting in a failed abortion was infrequent and did not significantly affect the safety and efficacy of medical abortion. Furthermore, because the process of expelling the pregnancy may begin as soon as 2 hours after taking misoprostol, there is a benefit in allowing patients to choose when and where to start this process, to maximize the possibility of their being at a safe place at a convenient time to experience cramping and bleeding.⁵⁵

In support of your assertion of significantly increased failure rates, you cite a pilot study by Lohr et al.⁵⁶ Lohr et al. assessed the complete abortion rate using simultaneous oral mifepristone and buccal misoprostol in three gestational age groupings (less than or equal to 49 days, 50-56 days, 57-63 days) and compared the rates with those published in previous pilot investigations⁵⁷ using simultaneous oral mifepristone and vaginal misoprostol in the same three gestational age groupings. The complete abortion rates reported by Lohr at 24 hours for oral mifepristone and buccal misoprostol were 72.5 percent, 69.2 percent, and 72.5 percent, respectively; the complete abortion rates at two weeks, however, were 97.5 percent, 100 percent, and 94.9 percent, respectively (and are consistent with the completion rates as described in the approved labeling).⁵⁸ The published complete abortion rates at 24 hours for simultaneous oral mifepristone and vaginal misoprostol administration were 90 percent, 88 percent, and 83 percent, respectively, for the gestational age groupings and the complete abortion rates at 2 weeks were 98 percent, 93 percent, 90 percent, respectively. Based on the data presented in Lohr,

⁵⁴ See 2016 Clinical Review, *supra* n. 13, at 41 and 48.

⁵⁵ *Id.* at 38.

⁵⁶ Petition at 7 (referencing Lohr PA, Reeves MF, Hayes JL, et al., 2007, Oral Mifepristone and Buccal Misoprostol Administered Simultaneously for Abortion: A Pilot Study, *Contraception*, 76:215-220).

⁵⁷ Schreiber CA, Creinin MD, Harwood B, Murthy AS. A pilot study of mifepristone and misoprostol administered at the same time for abortion in women with gestation from 50 to 63 days. *Contraception* 2005;71:447-50; Murthy AS, Creinin MD, Harwood B, Schreiber C. A pilot study of mifepristone and misoprostol administered at the same time for abortion up to 49 days gestation. *Contraception* 2005;71:333-6.

⁵⁸ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

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the use of buccal misoprostol at the same time as oral mifepristone does not adversely affect efficacy, although expulsion may be delayed. As recommended in Section 2.3 of the approved labeling, follow-up at 7-14 days after administration of mifepristone is more appropriate to evaluate efficacy.⁵⁹ It is misleading to only reference the abortion completion rates observed at the 24-hour timepoint from Lohr. Therefore, we do not agree that data from Lohr indicate higher failure rate with misoprostol taken before the prescribed minimum 24-hour period after taking mifepristone.

Although we disagree that Lohr demonstrates a higher failure rate with misoprostol taken before 24-hours after taking mifepristone, we note that our 2016 review of the S-020 efficacy supplement referenced a 2013 systematic review by Raymond, which concluded that if the interval between mifepristone and misoprostol interval is less than or equal to 24 hours, the procedure is less effective compared to an interval of 24-48 hours.⁶⁰ As explained above, the data reviewed in 2016 showed that Mifeprex, in a regimen with misoprostol administered at home, was safe and effective. Therefore, incorrect administration, if it occurred, was infrequent and did not significantly affect the safety and efficacy of medical abortion. However, in light of the data reviewed, section 2.1 of the labeling approved in 2016 (as well as the currently approved labeling and Medication Guide) states that there should be a “minimum 24-hour interval between” mifepristone and misoprostol (emphasis included in the labeling).⁶¹ The approved dosing regimen also states that misoprostol is taken within 24 to 48 hours after taking mifepristone and acknowledges that the effectiveness of the regimen may be lower if misoprostol is administered less than 24 hours after mifepristone administration.

In addition to your concerns that a woman may take misoprostol too soon after administering mifepristone, you also state that waiting until 24 hours after administering mifepristone does not guarantee success (Petition at 7-8). In support of this concern, you cite a 2015 review by Chen and Creinin. You state that this review found “women taking misoprostol earlier than 48 hours after Mifeprex are more likely to fail the regimen” (Petition at 8). Chen and Creinin included studies in which the intervals between mifepristone and buccal misoprostol were 24 hours or 24-48 hours and stated that “based on the available literature, the overall efficacy of regimens with a 24-hour interval between mifepristone and buccal misoprostol is significantly lower than those with a 24- to 48-hour interval (94.2 percent compared with 96.8 percent).”⁶² The rate differences were statistically significant, but both regimens were more effective than the 92 percent efficacy rate of the original regimen approved in 2000 (administering misoprostol 48 hours after taking mifepristone).

Finally, you also express concern that if misoprostol is self-administered, a woman may swallow it rather than keep the pill between her cheek and gum, and oral administration of

⁵⁹ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

⁶⁰ 2016 Clinical Review, supra n. 13, at 31 (citing 8 Raymond EG, et al. First-trimester medical abortion with mifepristone 200 mg and misoprostol: a systematic review. *Contraception* 2013;87(1):26-37.)

⁶¹ See https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

⁶² See Chen MJ and Creinin MD. Mifepristone with buccal misoprostol for medical abortion. *Obstet Gynecol.* 2015;126(1):12-21; see also 2016 Clinical Review, supra n. 13, at 21.

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misoprostol (i.e., swallowing the pill) following the lower dose of mifepristone in the current regimen is not as effective in ending the pregnancy (Petition at 7). Winikoff et al. specifically studied the use of oral compared to buccal misoprostol 24-36 hours after mifepristone 200 mg with overall success rates of 91.3 percent and 96.2 percent, respectively.⁶³ Both regimens resulted in a greater than 91 percent successful medical abortion. Although the study showed decreased efficacy with oral versus buccal administration in 57-63 days gestational age, there were no statistical differences in other gestational age groupings. Even assuming there is a small proportion of women who are 57-63 days gestational age and use oral administration of misoprostol (rather than buccal as labeled), a small decrease in the reported efficacy in that population would not justify requiring a clinic visit for all women undergoing medical abortion.

Overall, studies support the efficacy of the mifepristone, in a regimen with misoprostol when taken by the patient at home. Therefore, we do not agree that an in-person visit is necessary to manage administration of misoprostol.

iii. Rh-Negative Patients

In the Petition, you state that a follow-up examination is particularly critical for Rh-negative patients and that without that follow-up examination, women will not receive Rhogam after the abortion, increasing their risk of subsequent Rh isoimmunization, which can endanger future pregnancies (Petition at 9). You suggest that a clinic visit after the administration of Mifeprex is important for Rh-negative women to receive Rhogam and that removing the required follow-up visit puts Rh-negative women at risk for isoimmunization. We do not agree.

Rh testing is standard of care in the United States and RhD immunoglobulin (such as Rhogam) should be administered if indicated. Further, administration of RhD immunoglobulin should be given within 72 hours of a sensitizing event (e.g., medical abortion).⁶⁴ However, the facility where the RhD immunoglobulin injection occurs (clinic, hospital or laboratory) is not critical. A shift from medical clinics to hospitals for administration of injections has occurred over the years due to shortages of RhD immunoglobulin and poor reimbursement for RhD immunoglobulin injection from third-party payers.⁶⁵ This has resulted in pregnant women frequently obtaining routine 28-week RhD immunoglobulin injections at hospitals/laboratories with a prescription provided by their healthcare providers. This same process of obtaining RhD immunoglobulin via prescription is available to patients after medical termination of pregnancy and does not require a follow-up clinic visit.

⁶³ Winikoff B, Dzuba, IG, Creinin MD, et al, 2008, Two Distinct Oral Routes of Misoprostol in Mifepristone Medical Abortion, *Obstet Gynecol* 112(6):1303-1310.

⁶⁴ ACOG Practice Bulletin No. 181. Prevention of Rh D Alloimmunization. August 2017.

⁶⁵ See <https://www.mdedge.com/obgyn/article/61083/practice-management/rhogam-injections-payment-levels-vary-among-insurers>.

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In summary, the totality of data on the efficacy and safety of medical abortion at less than 70 days gestation, derived from numerous studies, has characterized the complications and rates of complications for completing medical abortion at home, and the findings show medical abortion at home is both safe and effective without three office visits. We therefore deny your request that the use of mifepristone in a regimen with misoprostol require three office visits by the patient.

c. Contraindications

In the Petition, you assert that critical language contraindicating Mifeprex for patients without access to appropriate emergency medical care was excluded from the 2016 Mifeprex labeling. You cite to a study⁶⁶ and ACOG statements as evidence that medical abortions have greater risks and more need for emergency “operation” than a surgical abortion, particularly for patients in rural areas with limited access to emergency medical care (Petition at 11).

Although inadequate access to medical facilities for appropriate care was removed from the list of contraindications in section 4 of the approved labeling when we approved the S-020 efficacy supplement, the 2016 Mifeprex labeling and the currently approved mifepristone labeling, as well as the Mifepristone REMS Program, continue to include appropriate instructions for providers regarding patient access to appropriate medical care.⁶⁷ For example, the Boxed Warning includes language directing healthcare providers to ensure that the patient knows whom to call and what to do, including potentially going to an emergency room, if the patient experiences serious events associated with the use of mifepristone. The labeling also directs healthcare providers, as part of the dosing regimen, to give the patient the name and phone number of a healthcare provider who will be handling emergencies.⁶⁸ In addition, one of the required qualifications listed in the Prescriber Agreement Form is the “[a]bility to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.”⁶⁹ Therefore, although certain language about access to medical facilities was removed from the approved labeling in 2016, we disagree that critical language about access to appropriate emergency medical care is lacking from the approved labeling.

⁶⁶ See Petition Reference Document No. 17 (Harrison Affidavit: Donna Harrison, M.D., Aff. *Okla. Coalition for Reproductive Justice v. Cline*, Case No. CV-2014-1886 (Feb. 24, 2015), ¶115 (referencing M. Niinimäki et al., Immediate Complications after Medical compared with Surgical Termination of Pregnancy, *Obstet. Gynecol.* 114:795 (Oct. 2009)).

⁶⁷ See Mifeprex labeling, approved 2016.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020687s020lbl.pdf. See also current labeling at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020687s022lbl.pdf.

⁶⁸ *Id.*

⁶⁹ Mifepristone REMS Program,

<https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=RemsDetails.page&REMS=390>.

Emphasis added.

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You also cite information in Box 1, Features of Medical and Surgical Abortion (page 3) in the ACOG Practice Bulletin No. 143.⁷⁰ As mentioned above, the ACOG Practice Bulletin No. 143 has been withdrawn and the language you cite is not included in the current Practice Bulletin No. 225.

d. Adverse Event Reporting

In the Petition, you assert that even under the regimen approved in 2000, it was difficult to collect accurate and complete adverse event information for Mifeprex, and that collecting such information is virtually impossible under the regimen approved in 2016 because prescribers only are required to report deaths associated with Mifeprex (Petition at 12). You also assert that FDA cannot adequately assess the safety of the current Mifeprex regimen without comprehensive information on adverse events (Petition at 12). You state that certified prescribers should at a minimum be required to report the following to FDA's MedWatch reporting system and to the sponsor: deaths, hospitalizations, blood transfusions, emergency room visits, failures requiring surgical completion, ongoing pregnancy, or other major complications, including detailed information on these events (Petition at 13).

We acknowledge that there is always a possibility with any drug that some adverse events are not being reported, because reporting to the Agency's MedWatch program by health care professionals and patients is voluntary. We do not agree, however, that the 2016 changes to the prescriber reporting requirements limit our ability to adequately monitor the safety of mifepristone for medical termination of pregnancy. Prior to the 2016 approval of the S-20 efficacy supplement, we assessed approximately 15 years of adverse event reports both from the Applicant and through the MedWatch program and determined that certain ongoing additional reporting requirements under the Mifeprex REMS, such as hospitalization and blood transfusions, were not warranted. This assessment was based on the well-characterized safety profile of Mifeprex, with known risks occurring rarely, along with the essentially unchanged safety profile of Mifeprex during this 15-year period of surveillance. Accordingly, the Prescriber Agreement Form was amended as part of our 2016 approval of the S-20 efficacy supplement to require, with respect to adverse event reporting, only that prescribers report any cases of death to the Applicant.

We also note that the reporting changes to the Prescriber Agreement Form as part of our 2016 approval do not change the adverse event reporting requirements for the Applicants. Like all other holders of approved NDAs and ANDAs, the Applicants are required to report all adverse events, including serious adverse events, to FDA in accordance with the requirements set forth in FDA's regulations (see 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81). FDA also routinely reviews the safety information provided by the Applicants in the Annual Reports. As with all drugs, FDA continues to closely monitor the postmarketing safety data on mifepristone for the medical termination of pregnancy.

⁷⁰ Petition at 11. Medical Management of First-Trimester Abortion. ACOG Practice Bulletin Number 143. March 2014 (Reaffirmed 2016. Replaces Practice Bulletin Number 67, October 2005); Obstet Gynecol. 2014 Mar;123(3):676-692 at 680.

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You state that FDA should provide guidance to emergency healthcare providers and physicians so that they know how to distinguish complications following drug-induced abortion from complications following spontaneous miscarriage (Petition at 13). We disagree that specific guidance is needed at this time. In the past, when appropriate, FDA has worked with the NDA Applicant to issue communications to healthcare providers and emergency department providers concerning certain serious adverse events.⁷¹ Furthermore, the approved Medication Guide advises patients to take the Medication Guide with them if they need to go to the emergency room or seek care from a healthcare provider other than the one who dispensed the medication to them, so the emergency room or healthcare provider understands the patient is having a medical abortion. We have not identified a change in the safety profile of mifepristone that would warrant additional communications to healthcare providers and emergency department providers concerning complications following medical abortion. If we become aware of safety information that merits further communications with emergency department providers or healthcare providers, or that warrants revisions to the approved labeling, we will act as appropriate.

You also assert that many Mifeprex prescribers “violate FDA protocol,” instructing their patients to lie to emergency medical personnel, and that this prevents emergency healthcare providers from appropriately caring for their patients and further decreases the likelihood that adverse events will be reported (Petition at 12). Your only support for this claim is a reference to instructions from the organization Aid Access⁷² to patients that they can tell emergency room staff that they had a miscarriage and do not need to tell medical staff that they had a medical abortion. The Petition does not provide any data or additional information establishing “many Mifeprex prescribers violate FDA protocol, instructing their patients to lie,” or that these providers thereby prevented appropriate care and decreased the number of adverse events reported.

B. REMS

1. Request to Retain Mifeprex REMS

In your Petition, you request that FDA retain the Mifeprex REMS (Petition at 14). We agree that a REMS is necessary to ensure that the benefits of mifepristone in a regimen with misoprostol outweigh the risks. FDA’s determination as to whether a REMS is necessary

⁷¹ See Historical Information on Mifepristone (Marketed as Mifeprex), available at <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111334.htm>. For example, the NDA applicant and FDA agreed that there was a need to issue a Dear Health Care Provider letter in April 2002 and a Dear Emergency Room Director letter in September 2004. The fact that these letters were issued does not imply that the approved mifepristone regimen is unsafe; it is not uncommon for drug sponsors to issue “Dear Health Care Provider” letters, and, as noted in the Mifepristone Q&A document posted on our Web site in April 2002, “[w]hen FDA receives and reviews new information, the agency provides appropriate updates to doctors and their patients so that they have essential information on how to use a drug safely.”

⁷² We note that Aid Access facilitated the sale of unapproved mifepristone and misoprostol to U.S. consumers and that FDA sent Aid Access a warning letter asking it to promptly cease causing the sale of unapproved and misbranded drugs to U.S. consumers. US FDA Warning Letter to Aidaccess.org, dated March 8, 2019. <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/aidaccessorg-575658-03082019>.

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to ensure that the benefits of a drug outweigh its risks is a complex, drug-specific inquiry, reflecting an analysis of multiple, interrelated factors and of how those factors apply in a particular case.⁷³ In conducting this analysis, FDA considers whether (based on premarketing or postmarketing risk assessments) there is a particular risk or risks associated with the use of the drug that, on balance, outweigh its benefits and whether additional interventions beyond FDA-approved labeling are necessary to ensure that the drug's benefits outweigh its risks.⁷⁴

As described in the background section of this response (see section I.A.), FDA determined that interventions in addition to the FDA-approved labeling were necessary to ensure that the benefits of Mifeprex outweighed its risks when the drug was initially approved in 2000, and periodic re-evaluations of the REMS since that time have reached the same conclusion. As further described in the background section of this response (see section I.E.), FDA recently undertook a review of the Mifepristone REMS Program. As explained below, the Mifepristone REMS Program continues to be necessary to ensure the benefits outweigh the risks.

After review of multiple different sources of information, including published literature, safety information submitted to the Agency during the COVID-19 PHE, FAERS reports, the first REMS assessment report for the Mifepristone REMS Program, and information provided by advocacy groups, individuals, and the Plaintiffs in ongoing litigation,⁷⁵ as well as information submitted by the Applicants, we have concluded that the REMS can be modified to reduce the burden on the health care delivery system without compromising patient safety. As explained below, we agree that the healthcare provider certification (ETASU A) and dispensing of mifepristone to patients with evidence or other documentation of safe use conditions (ETASU D) continue to be necessary components of the REMS to ensure the benefits outweigh the risks. However, we have concluded that the Mifepristone REMS Program must be modified to remove the requirement under ETASU C that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals.

Below, we discuss each of these elements of the Mifepristone REMS Program.

a. ETASU A – Prescriber Certification/Qualifications

ETASU A under the Mifepristone REMS Program requires healthcare providers who prescribe mifepristone to be certified. In order to become certified, prescribers must: 1) review the prescribing information for mifepristone and 2) complete the Prescriber Agreement Form. In signing the Prescriber Agreement Form, prescribers agree they meet the qualifications listed below:

⁷³ See FDA Guidance for Industry, *REMS: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary* (Apr. 2019).

⁷⁴ *Id.*

⁷⁵ See *supra* n. 10.

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- Ability to assess the duration of pregnancy accurately
- Ability to diagnose ectopic pregnancies
- Ability to provide surgical intervention in cases of incomplete abortion or severe bleeding, or to have made plans to provide such care through others, and ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary.
- Has read and understood the Prescribing Information of mifepristone (which the provider can access by phone or online).

In addition to meeting these qualifications, as a condition of certification the healthcare provider also agrees to follow the guidelines for use below:

- Review the Patient Agreement Form with the patient and fully explain the risks of the mifepristone treatment regimen. Answer any questions the patient may have prior to receiving mifepristone.
- Sign and obtain the patient's signature on the Patient Agreement Form.
- Provide the patient with a copy of the Patient Agreement Form and the Medication Guide.
- Place the signed Patient Agreement Form in the patient's medical record.
- Record the serial number from each package of mifepristone in each patient's record.
- Report deaths to the Applicant, identifying the patient by a non-identifiable patient reference and the serial number from each package of mifepristone.

Our review of the published literature did not identify any studies comparing healthcare providers who met these qualifications with healthcare providers who did not. In the absence of such studies, there is no evidence to contradict our previous finding that prescribers' ability to accurately date pregnancies, diagnose ectopic pregnancies, and provide surgical intervention either personally or through others, is necessary to mitigate the serious risks associated with the use of mifepristone in a regimen with misoprostol. Therefore, our conclusion continues to be that a healthcare provider who prescribes mifepristone in a regimen with misoprostol should meet the above qualifications. Absent these provider qualifications, we are concerned that serious and potentially fatal complications associated with medical abortion, including missed ectopic pregnancy and heavy bleeding from incomplete abortion, may not be detected or appropriately managed.

Accordingly, we have determined that ETASU A must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks. Maintaining the requirement for prescriber certification ensures that providers meet the necessary qualifications and adhere to the guidelines for use listed above. The burden of prescriber certification has been minimized to the extent possible by requiring prescribers to certify only one-time for each applicant.

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Although we agree with your request to retain the REMS for mifepristone (now the Mifepristone REMS Program) insofar as it pertains to ETASU A, as discussed in section II.A.2.a of this response, we do not agree with your request that the healthcare provider needs to be a licensed physician to meet this requirement.

b. ETASU D – Requirement For The Drug To Be Dispensed With Evidence Or Other Documentation Of Safe-Use Conditions

ETASU D under the Mifepristone REMS Program requires mifepristone to be dispensed with evidence or other documentation of safe-use conditions. To receive mifepristone for medical termination of intrauterine pregnancy through 70 days gestation, the patient must sign a Patient Agreement Form indicating that the patient has received, read, and been provided a copy of the Patient Agreement Form and received counseling from the prescriber regarding the risk of serious complications associated with mifepristone for this indication. The Patient Agreement Form ensures that patients are informed of the risks of serious complications associated with mifepristone for this indication. In a number of approved REMS, Patient Agreement Forms or Patient Enrollment Forms ensure that patients are counseled about the risks of the product and/or informed of appropriate safe use conditions.⁷⁶

As a condition of certification under the Mifepristone REMS Program, healthcare providers must follow the guidelines for use of mifepristone, including reviewing the Patient Agreement Form with the patient, fully explaining the risks of the treatment regimen and answering any questions the patient may have before receiving the medication. With this form, the patient acknowledges that they have received and read the form, and that they have received the counseling regarding when to take mifepristone, the risk of serious complications associated with mifepristone and what to do if they experience adverse events (e.g., fever, heavy bleeding). Both the healthcare provider and patient must sign the document and the patient must receive a copy of the signed form. In addition to the counseling described in the Patient Agreement Form, patients also receive a copy of the Medication Guide for mifepristone. Ultimately, the Patient Agreement Form serves as an important counseling component, and documentation that the safe use conditions of the Mifepristone REMS Program have been satisfied, as the prescriber is required to place the signed Patient Agreement Form in the patient's medical record.

In addition, we conducted an updated review of published literature since 2016 to assess the utility of maintaining the Patient Agreement Form as part of the Mifepristone REMS Program, and these studies do not provide evidence that would support removing ETASU D. For these reasons, we have determined that ETASU D must remain an element of the Mifepristone REMS Program to ensure the benefits outweigh the risks.

⁷⁶ REMS@FDA, <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>, Accessed November 15, 2021.

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c. ETASU C – In-Person Dispensing

ETASU C under the Mifepristone REMS Program currently requires mifepristone to be dispensed to patients only in certain healthcare settings, specifically clinics, medical offices, and hospitals, by or under the supervision of a certified prescriber. This creates what we refer to in this response as an in-person dispensing requirement under the REMS; i.e., the patient must be present in person in the clinic, medical office, or hospital when the drug is dispensed. The mifepristone REMS document currently states that mifepristone may not be distributed to or dispensed through retail pharmacies or settings other than a clinic, medical office, or hospital. As explained below, based on a recent review of the REMS, we believe that the Mifepristone REMS Program must be modified to remove the requirement that mifepristone be dispensed only in certain healthcare settings, specifically clinics, medical offices, and hospitals, because this requirement is no longer necessary to ensure that the benefits of the drug outweigh the risks. This conclusion is based on our review of information from the Mifepristone REMS Program one-year (1st) REMS⁷⁷ assessment data and postmarketing safety information, and supported by our review of the published literature.

i. Assessment Data

As part of our review of the REMS, we evaluated information included in the 1st REMS assessment report for the Mifepristone REMS Program, which included healthcare provider certification data, program utilization data, and non-compliance data. This 1st REMS assessment report covers a reporting period between April 11, 2019 through February 29, 2020. During this reporting period, a small number of non-compliance events were reported.

As described in section I.C. of this response, during the timeframe from January 27, 2020 through September 30, 2021, there were periods when the in-person dispensing requirement was not enforced. To better understand whether there was any impact on safety or non-compliance during the periods when the in-person dispensing requirement was not enforced, we requested additional information from the Applicants to provide for more comprehensive assessment of the REMS for the time period from January 27, 2020 (the effective date of the COVID-19 PHE) to September 30, 2021. We requested the Applicants provide a summary and analysis of any program deviation or non-compliance events from the REMS requirements and any adverse events that occurred during this time period that had not already been submitted to FDA. The NDA and the ANDA Applicants reported a total of eight cases reporting adverse events between January 27, 2020 and September 30, 2021. These eight cases were also identified in the FAERS database and are described below.

The number of adverse events reported to FDA during the COVID-19 PHE with mifepristone use for medical termination of pregnancy is small, and the data provide no

⁷⁷ This REMS assessment report was the first submitted following the approval of the single, shared system REMS for mifepristone.

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indication that any program deviation or noncompliance with the Mifepristone REMS Program contributed to these reported adverse events.

ii. FAERS/Postmarketing Safety Data

FDA routinely monitors postmarketing safety data for approved drugs through adverse events reported to our FAERS database,⁷⁸ through our review of published medical literature, and when appropriate, by requesting applicants submit summarized postmarketing data. For our recent review of the REMS, we searched our FAERS database, reviewed the published medical literature for postmarketing adverse event reports for mifepristone for medical termination of pregnancy, and requested that the Applicants submit a summary and analysis of certain adverse events. Our review of this postmarketing data indicates there have not been any new safety concerns with the use of mifepristone for medical termination of pregnancy through 70 days gestation, including during the time when in-person dispensing was not enforced.

In order to evaluate the periods when in-person dispensing was and was not enforced, we conducted a search of the FAERS database and the published medical literature to identify U.S. postmarketing adverse events that reportedly occurred from January 27, 2020 through September 30, 2021 with mifepristone use for medical termination of pregnancy. The data for this time period were then further divided into the date ranges when in-person dispensing was enforced per the REMS (January 27, 2020 - July 12, 2020 and January 13, 2021 - April 12, 2021) versus when in-person dispensing was not enforced: July 13, 2020 - January 12, 2021 (in-person dispensing enforcement was temporarily enjoined) and April 13, 2021 - September 30, 2021 (enforcement discretion for in-person dispensing because of the COVID-19 PHE).

Based on the above search, a total of eight cases were identified in FAERS and no additional case reports were identified in the medical literature. Two of the eight cases reported adverse events that occurred when in-person dispensing was being enforced (i.e., January 27, 2020-July 12, 2020 and January 13, 2021-April 12, 2021). These two cases reported the occurrence of uterine/vaginal bleeding (case 1) and uterine/vaginal bleeding and sepsis (case 2). Of note, uterine/vaginal bleeding and sepsis are labeled adverse events. Five of the eight cases reported adverse events that occurred when in-person dispensing was not enforced (i.e., July 13, 2020-January 12, 2021 and April 13, 2021-September 30, 2021); however, the narratives provided in the FAERS reports for three of the five cases explicitly stated that mifepristone was dispensed in-person. These five cases reported the occurrence of ongoing pregnancy (case 3), drug intoxication and death approximately 5 months after ingestion of mifepristone (case 4), death [cause of death is currently unknown] (case 5), sepsis and death (case 6), and pulmonary embolism (case 7). Of note, ongoing pregnancy and sepsis, including the possibility of fatal septic shock, are labeled adverse events. The remaining case reported the occurrence of oral pain/soreness (case 8) in July

⁷⁸ FAERS is a database that contains adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA. The database is designed to support FDA's post-marketing safety surveillance program for drug and therapeutic biologic products.

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2021, but did not provide sufficient information to determine the exact date of the adverse event.

As discussed in section II.A.2.d., the Applicants report adverse events, including serious adverse events, to FDA in accordance with applicable regulations.⁷⁹ To enable additional review of adverse events, Applicants were requested to provide a summary and analysis for adverse events reported with incomplete medical abortion requiring surgical intervention to complete abortion, blood transfusion following heavy bleeding or hemorrhage, ectopic pregnancies, sepsis, infection without sepsis, hospitalization related to medical abortion, and emergency department/urgent care encounter related to medical abortion. The Applicant for Mifeprex provided the requested summary of postmarketing safety information from March 29, 2016, when S-020 was approved, through September 30, 2021. The Applicant for the generic provided the requested summary of postmarketing safety information from April 11, 2019 (date of initial approval) through September 30, 2021. The information provided by the Applicants included the same cases identified in FAERS, as discussed above.

We analyzed the FAERS data referenced above to determine if there was a difference in adverse events when in-person dispensing was and was not enforced. Based on FDA's review of this data, we concluded that there does not appear to be a difference in adverse events when in-person dispensing was and was not enforced and that mifepristone may be safely used without in-person dispensing. FDA's review of the summary and analysis data submitted by the Applicants (which, as noted above, included the same cases identified from FAERS) did not change this conclusion.

iii. Published Literature

As noted above, we also conducted an extensive review of the published literature since March 29, 2016 (the date the S-020 efficacy supplement for Mifeprex was approved) through September 30, 2021.⁸⁰ Published studies have described alternatives in location and method for dispensing mifepristone by a certified prescriber (or equivalent healthcare provider in countries other than the United States). Some studies have examined replacing in-person dispensing in certain healthcare settings with dispensing at retail pharmacies⁸¹

⁷⁹ See 21 CFR 314.98, 21 CFR 314.80, and 21 CFR 314.81.

⁸⁰ In support of your request that we retain the REMS and continue limiting the dispensing of Mifeprex to patients in clinics, medical offices, and hospitals by or under the supervision of a certified prescriber, you reference two studies that you assert do not comply with the REMS (Petition at 19-22). Outcomes from both of the studies you reference have been reported in the published literature and are addressed in the discussion that follows. We note that as a general matter, a clinical investigation of an approved drug that is subject to a REMS can take place in healthcare settings outside those provided for in the REMS. When an approved drug that is subject to a REMS is studied in a clinical trial, the REMS does not apply to the use of the drug in that clinical trial. However, FDA reviews the protocol to ensure that it will be conducted in a manner that adequately addresses the risks that the REMS is intended to mitigate, such that the trial participants will not be exposed to an unreasonable and significant risk of illness or injury. See 21 CFR 312.42(b)(1)(i) and (b)(2)(i).

⁸¹ Grossman D, Baba CF, Kaller S, et al. Medication Abortion With Pharmacist Dispensing of Mifepristone. *Obstet Gynecol* 2021;137:613–22; Rocca CH, Puri M, et al. Effectiveness and safety of early medication

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and dispensing mifepristone from pharmacies by mail.⁸² Other studies have evaluated two modes of dispensing by prescribers: (1) prescribers mailing the medications to patients,⁸³ and (2) prescribers using couriered delivery of medications.⁸⁴ Different studies have evaluated dispensing mifepristone by mail by an entity described as “a partner organization.”⁸⁵

We note that the ability to generalize the results of these studies to the United States population is hampered by differences between the studies with regard to pre-abortion care (e.g., telemedicine versus in-person). In addition, the usefulness of the studies is limited in some instances by small sample sizes and lack of follow-up information on outcomes with regard to both safety and efficacy. There are also factors which complicate the analysis of the dispensing element alone. Some of these factors are: (1) only a few studies have evaluated alternatives for in-person dispensing of mifepristone in isolation (for example, most studies on mail dispensing of mifepristone also include telemedicine consultation); and (2) because most serious adverse events with medical abortion are infrequent, further evaluation of changes in dispensing would require studies with larger numbers of participants. We did not find any large clinical studies that were designed to collect safety outcomes in healthcare systems similar to the United States. Despite the limitations of the studies we reviewed, we have concluded that overall the outcomes of these studies are not inconsistent with our conclusion that, based on the 1st year REMS assessment report and postmarketing safety data, mifepristone will remain safe and efficacy will be maintained if the in-person dispensing requirement is removed from the Mifepristone REMS Program.

abortion provided in pharmacies by auxiliary nurse-midwives: A non-inferiority study in Nepal. *PLoS ONE* 13(1): e0191174. <https://doi.org/10.1371/journal.pone.0191174>; Wiebe ER, Campbell M, et al. Comparing telemedicine to in-clinic medication abortions induced with mifepristone and misoprostol. *Contracept X*. 2020; 2: 100023.

⁸² Grossman D, Raifman S, Morris N, et.al. Mail-order pharmacy dispensing of mifepristone for medication abortion after in-person clinical assessment. *Contraception* 2021, ISSN 0010-7824, <https://doi.org/10.1016/j.contraception.2021.09.008>, Available online 20 September 2021; Upadhyay UD, Koenig LR, Meckstroth KR. Safety and Efficacy of Telehealth Medication Abortion in the US During the COVID-19 Pandemic. *JAMA Network Open*. 2021;4(8):e2122320, doi:10.1001/jamanetworkopen.2021.22320; Hyland P, Raymond EG, Chong E. A direct-to-patient telemedicine abortion service in Australia: Retrospective analysis of the first 18 months. *Aust N Z J Obstet Gynaecol* 2018;58: 335-340.

⁸³ See Anger HA, Raymond EG, et al. Clinical and service delivery implications of omitting ultrasound before medication abortion provided via direct-to-patient telemedicine and mail. *Contraception* 2021 Jul 28;S0010-7824(21)00342-5. doi: 10.1016/j.contraception.2021.07.108. Published online. Raymond E, Chong E, et al. TelAbortion: evaluation of a direct to patient telemedicine abortion service in the United States. *Contraception* 2019; 100:173-177. See also Chong et al., *infra* n. 103 Kerestes et al., *infra* n. 105, and Aiken et al., *infra* n. 106.

⁸⁴ Reynolds-Wright JJ, et al. *BMJ Sex Reprod Health* 2021;0:1–6. doi:10.1136/bmj.srh-2020-200976.

⁸⁵ Endler M, Beets L, Gemzell Danielsson K, Gomperts R. Safety and acceptability of medical abortion through telemedicine after 9 weeks of gestation: a population-based cohort study. *BJOG* 2019;126:609-618. Norton H, Ilozumba O, Wilkinson J, Gemzell Danielsson K, Gomperts R. 10-year evaluation of the use of medical abortion through telemedicine: a retrospective cohort study. *BJOG* 2021; <https://doi.org/10.1111/1471-0528.16765>; Aiken ARA, Digol I, Trussell J, Gomperts R. Self-reported outcomes and adverse events after medical abortion through online telemedicine: population based study in the Republic of Ireland and Northern Ireland. *BMJ* 2017;357:j2011 <http://dx.doi.org/10.1136/bmj.j2011>.

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Below is a summary of our review of the literature, organized by the methods of dispensing mifepristone that were studied.

(a) Retail pharmacy dispensing

Three studies reported medical abortion outcomes for retail pharmacy dispensing of mifepristone after clinical evaluation (Grossman,⁸⁶ Rocca,⁸⁷ Wiebe⁸⁸). Grossman conducted a US-based study in which mifepristone and misoprostol were dispensed from a pharmacy partnered with the clinic. Complete abortion without additional procedures occurred in 93.5 percent of participants with known outcomes. The reported proportion of complete abortion is within the range described in the approved mifepristone labeling. No participants experienced a serious adverse event, were hospitalized or required transfusion. Three participants had emergency department (ED) visits with treatment (intravenous hydration, pain medication, pelvic infection after uterine aspiration for incomplete abortion). The study safety and efficacy outcomes are consistent with labeled outcome frequencies. The study has limited generalizability because it was conducted in two US states and involved partnered pharmacies, some of which were in the same building as the clinic. Additionally, all participating pharmacies in this study were required to have a pharmacist on duty during clinic hours who had been trained in the study protocol and was willing to dispense mifepristone. The study conditions may not be generalizable to United States retail pharmacies; there is insufficient information to assess this.

Rocca⁸⁹ conducted an observational study evaluating participants who obtained medical abortions in Nepal by comparing the provision of medical abortion service by newly trained nurse midwives in pharmacies to medical abortion provided in government-certified clinics. The authors reported that, with respect to complete abortion (greater than 97 percent) and complications (no hospitalizations or transfusions), evaluation and dispensing in pharmacy was non-inferior to in-clinic evaluation and dispensing.

Wiebe,⁹⁰ in a retrospective, chart review study conducted in Canada, compared abortion outcomes of women who underwent medical abortion with telemedicine consult, and either received medications by courier or picked them up at a local pharmacy, with outcomes of a matched control cohort of women who received the medications at a pharmacy after an in-clinic visit. The groups had similar documented complete medical abortion outcomes (equal to or greater than 95 percent participants with known outcomes). The telemedicine group had one case of hemorrhage (0.5 percent) and one case of infection requiring antibiotics (0.5 percent) compared with no cases of hemorrhage or infection requiring antibiotics in the in-clinic cohort. The telemedicine group had more ED visits (3.3 percent compared to 1.5 percent in-clinic cohort). Both models of dispensing mifepristone resulted in efficacy and safety outcomes within labeled frequency.

⁸⁶ Grossman et al., supra n. 81.

⁸⁷ Rocca et al., supra n. 81.

⁸⁸ Wiebe et al., supra n. 81.

⁸⁹ Rocca et al., supra n. 81.

⁹⁰ Wiebe et al., supra n. 81.

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None of the three studies allow a determination regarding differences in safety between in-person dispensing by a certified prescriber in a health care setting and dispensing through a retail pharmacy, due to limitations on the generalizability of the results of the studies to the current retail pharmacy environment in the United States. The outcome findings from the one United States study (Grossman)⁹¹, in which the pharmacies were partnered with prescribers, are unlikely to be broadly generalizable to the current retail pharmacy environment and do not reflect typical prescription medication availability with use of retail pharmacy dispensing. For the retail pharmacy dispensing study in Canada (Wiebe),⁹² timely provision of medication from the retail pharmacy was accomplished by either courier to the woman or faxed prescription to the woman's pharmacy. It is unknown whether conditions that would allow timely access to medications for medical abortion would occur in retail pharmacies throughout the United States, suggesting the findings from that study may not be broadly generalizable. The third study (Rocca)⁹³ evaluated medical abortion provided in Nepali pharmacies and essentially moved the abortion provider and clinical examination into the pharmacy, a scenario that is not, at this time, applicable to the United States retail setting.

(b) Mail order pharmacy

Three studies evaluated mail order pharmacy dispensing (Grossman,⁹⁴ Upadhyay,⁹⁵ Hyland⁹⁶). Grossman published an interim analysis of an ongoing prospective cohort study evaluating medical abortion with mifepristone and misoprostol dispensed by mail-order pharmacy after in-person clinical assessment. Complete abortion without additional procedures occurred in 96.9 percent of participants with known outcomes. Two (0.9 percent) participants experienced serious adverse events; one received a blood transfusion and one was hospitalized overnight. Nine (4 percent) participants attended 10 ED visits. In this interim analysis, the outcomes are consistent with labeled frequencies.

Upadhyay⁹⁷ reports findings from a retrospective cohort study of women undergoing medical abortion in the United States without a consultation or visit. Eligibility was assessed based on a participant-completed online form collecting pregnancy and medical history. Participants who were considered eligible received medication delivered by a mail-order pharmacy. Abortion outcome was determined by either an assessment on day 3 or a 4-week pregnancy test. The investigators reported a complete abortion rate without additional procedures of 95 percent for participants with known outcomes and stated that no participants had any major adverse events. The proportion of abortion outcomes assessed at 3 days versus 4 weeks is not reported. Regardless, determining outcomes at 3 days is insufficient to determine outcome rates or safety findings because a 3-day follow-up period is too short. As recommended in Section 2.3 of the approved labeling, follow-up at

⁹¹ Grossman et al., supra n. 81.

⁹² Wiebe et al., supra n. 81.

⁹³ Rocca et al., supra n. 81.

⁹⁴ Grossman et al., supra n. 82.

⁹⁵ Upadhyay et al., supra n. 82.

⁹⁶ Hyland et al., supra n. 82.

⁹⁷ Upadhyay et al., supra n. 82.

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7-14 days after administration of mifepristone is more appropriate to evaluate safety and efficacy. This study used a model with numerous deviations from standard provision of medical abortion in the United States, such as no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history. These deviations, limited follow-up information, and small sample size limit the usefulness of this study.

Hyland⁹⁸ describes findings from a cohort study in Australia evaluating medical abortion outcomes utilizing telemedicine and a central mail order pharmacy. Complete abortions without additional procedures occurred in 96 percent of participants with documented outcomes and is consistent with labeled efficacy. Of the participants included in the analysis, 95 percent had no face-to-face clinical encounters after medications were mailed while 3 percent were admitted to the hospital and 2 percent had an outpatient encounter. One participant who was hospitalized and underwent a surgical uterine evacuation received a transfusion. Not included in the findings are 7 hospitalizations occurring in 7 participants who did not have “full follow up.” The authors do not report any other adverse events and conclude use of the telemedicine medical abortion service is safe. However, the reasons for hospitalization are not discussed by the authors; therefore, it is unknown why the patients were hospitalized. Although the reported frequency of hospitalizations (3 percent) is higher than the less than 1 percent in the FDA-approved mifepristone labeling, conclusions on the safety findings cannot be made in the absence of information about the reasons for hospitalization. Other limitations of this study include incomplete information about outcomes with face-to-face encounters.

Overall, the three studies evaluating mail order pharmacy dispensing suggest that efficacy of medical abortion is maintained with mail order pharmacy dispensing. With respect to safety, in the Grossman study⁹⁹ the interim analysis, although small, does not raise serious safety concerns. Safety findings from the Hyland¹⁰⁰ study are difficult to interpret. Although only one transfusion is reported and the authors state the findings demonstrate safety, a higher hospitalization rate and lack of information on the reasons for hospitalization preclude reaching any conclusions about the safety findings. Lastly, the Upadhyay¹⁰¹ study had no reported adverse events, but the findings are less useful because of the limited follow-up, and because medical abortions were provided using a model with numerous deviations from standard provision of medical abortion in the United States.

(c) Clinic dispensing by mail

A total of five studies evaluated clinic dispensing by mail. Gynuity Health Projects conducted a prospective cohort study (the “TelAbortion” study) evaluating use of telemedicine for remote visits and mifepristone being dispensed from clinics via overnight or regular tracked mail. Three publications reviewed have reported outcomes for the Gynuity population exclusively: Raymond (outcomes from May 2016 to December

⁹⁸ Hyland et al., supra n. 82.

⁹⁹ Grossman et al., supra n. 82.

¹⁰⁰ Upadhyay et al., supra n. 82.

¹⁰¹ Hyland et al., supra n. 82.

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2018),¹⁰² Chong (outcomes from May 2016 to September 2020)¹⁰³ and Anger (outcomes from March 2020 to September 2020).¹⁰⁴ A fourth study, Kerestes,¹⁰⁵ reports outcomes of medical abortion at the University of Hawai'i from April 2020 to November 2020 and a fifth study, Aiken (2021)¹⁰⁶ reports outcomes of medical abortion up to 70 days gestational age in the United Kingdom before and during the COVID-19 PHE in a retrospective cohort study.

In Raymond,¹⁰⁷ complete abortion without additional procedures occurred in 93 percent of participants with known outcomes. There were two hospitalizations (one participant received a transfusion for severe anemia despite having had a complete abortion) and 7 percent of participants had clinical encounters in ED/urgent care centers. The reported outcomes are similar to outcomes described in approved labeling except the combined ED/urgent care center encounters (7 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).¹⁰⁸ Of note, the authors state that half of the ED/urgent care visits did not entail any medical treatment. In Chong,¹⁰⁹ approximately 50 percent of the medical abortions occurred during the period of the COVID-19 PHE. Complete abortion without an additional procedure occurred in 95 percent of those with known outcomes. Transfusions were 0.4 percent and hospitalizations were 0.7 percent; 6 percent of participants had unplanned clinical encounters in ED/urgent care. Surgical interventions were required in 4.1 percent to complete abortion. The reported outcomes in Chong (which updated the findings described in Raymond) are similar to outcomes described in approved labeling except that (as with the Raymond study it updated) the combined ED/urgent care center encounters (6 percent) exceeded the ED visits in approved labeling (2.9-4.6 percent).

Anger,¹¹⁰ which compared outcomes among participants enrolled in the Gynuity study who did ("test medical abortion cohort") versus did not ("no-test medical abortion cohort")¹¹¹

¹⁰² Raymond et al., *supra* n. 83.

¹⁰³ Chong E, Shochet T, et al. Expansion of a direct-to-patient telemedicine abortion service in the United States and experience during the COVID-19 pandemic. *Contraception* 2021;104:43-48.

¹⁰⁴ Anger et al., *supra* n. 83.

¹⁰⁵ Kerestes C, Murayama S, et al. Provision of medication abortion in Hawai'i during COVID-19: Practical experience with multiple care delivery models. *Contraception* 2021 Jul;104(1):49-53. doi:10.1016/j.contraception.2021.03.025. Epub 2021 Mar 28.

¹⁰⁶ Aiken ARA, Lohr PA, et al. Effectiveness, safety and acceptability of no-test medical abortion (termination of pregnancy) provided via telemedicine: a national cohort study. *BJOG* 2021;128:1464-1474.

¹⁰⁷ Raymond, *supra* n. 83.

¹⁰⁸ The authors reported the combined frequency of emergency department/urgent care visits, whereas the approved labeling includes the frequency for emergency department (emergency room) visits. Therefore it is unknown whether the frequency of emergency department visits in the trial, as distinct from the combined frequency of emergency department/urgent care visits, is comparable to the frequency of emergency department visits reflected in approved labeling.

¹⁰⁹ Chong et al., *supra* n. 103.

¹¹⁰ Anger et al., *supra* n. 83.

¹¹¹ "No-test medication abortion" refers to medical abortion provided without a pretreatment ultrasound, pelvic examination or laboratory tests when, in the judgment of the provider, doing so is medically appropriate (appropriateness based on history and symptoms); "no-test medication abortion" does include post-abortion follow up. A sample protocol is described by Raymond et al." (Raymond EG, Grossman D, Mark A, et.al. Commentary: No-test medication abortion: A sample protocol for increasing access during a pandemic and beyond. *Contraception* 2020;101:361-366)

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have confirmation of gestational age/intrauterine location with an examination or ultrasound, found that those without an examination or ultrasound prior to medical abortion were more likely to require procedural interventions and had more unplanned clinical encounters.¹¹² There were no reported ectopic pregnancies in either group. The number of ED/urgent care visits and the proportion of unplanned clinical encounters that led to medical treatment were not reported. In the “test” group, complete medical abortion was confirmed in 98 percent of participants with known outcomes; one participant was “hospitalized and/or blood transfusion” and 8 percent had an unplanned clinic encounter (participant sought in-person medical care related to abortion and the visit was not planned prior to abortion). In the “no-test” group, complete medical abortion was confirmed in 94 percent of participants with known outcomes; two participants were “hospitalized and/or blood transfusion” and 12.5 percent had an unplanned clinical encounter.

Kerestes¹¹³ included three different delivery models: traditional in-person visits, telemedicine consultation with in-person pick-up of medications, and telemedicine consultation with delivery of medications by mail (most of the latter were enrolled through Gynuity’s TelAbortion study). Among participants with follow-up data, the rates of successful medical abortion without surgery were consistent with outcomes in approved labeling. Blood transfusion was given to two participants (both in the telemedicine plus in-person pickup group). Although ED visits occurred the most frequently in the telemedicine plus mail group (four participants or 5.8 percent) and the least in the in-person group (two participants or 2.1 percent), the study reported no increases in other serious adverse events. Aiken (2021)¹¹⁴ reported outcomes before and during the pandemic in a retrospective cohort study in the United Kingdom. The study compared the two cohorts: one before the pandemic with in-person visits and dispensing (traditional model) and one during the pandemic with either an in-person visit and in-person dispensing or a telemedicine visit and dispensing by mail or picked up from the clinic (hybrid model). Complete abortion occurred in greater than 98 percent in both cohorts; the rate was slightly higher in the telemedicine group than in the in-person group. There were no significant differences in the rates of reported serious adverse events. The investigators’ analysis determined that the efficacy and safety were comparable between both cohorts and concluded the hybrid model for medical abortion is effective and safe.

Taken together, data from the three Gynuity study reports (Raymond, Chong, and Anger), Kerestes, and Aiken (2021) support that efficacy of medical abortion was maintained when mifepristone was dispensed by mail from the clinic. Study reports of Raymond, Chong, and Kerestes all suggest there may be an increase in ED/urgent care visits with telemedicine visits and dispensing by mail from the clinic, but without increases in other serious adverse events. Anger’s comparative analysis suggests a pre-abortion examination may decrease the occurrence of procedural intervention and decrease the number of unplanned visits for postabortion care. The Aiken (2021) study appears to be of sufficient

¹¹² We note that the two cohorts were not randomized in the Anger study; they had different baseline characteristics. Consequently, findings based on the comparisons between the two cohorts should be interpreted carefully.

¹¹³ Kerestes et al., *supra* n. 105.

¹¹⁴ Aiken et al., *supra* n. 106.

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sample size to determine whether safety outcomes with mail dispensing differ from in-person dispensing; however, significant limitations include that the analysis was based on deidentified information and the investigators were unable to verify the outcomes extracted. Further, the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

Notwithstanding the limitations discussed above, these studies overall support that dispensing by mail from the clinic is safe and effective. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other serious adverse events related to mifepristone use.

(d) Clinic dispensing by courier

Reynolds-Wright¹¹⁵ reported findings from a prospective cohort study of participants at less than 12 weeks gestational age in Scotland undergoing medical abortion at home that provided mifepristone for pick up at the service or by couriered delivery to woman's home. The outcomes from this study in Scotland are consistent with the outcomes in the approved mifepristone labeling. However, the number of couriered deliveries was not reported. Thus this study does not provide abortion outcomes separately for couriered delivery of mifepristone and misoprostol. The study shares the same limitations as the Aiken (2021) study; the study's design did not capture all serious safety outcomes, thus limiting the certainty of the findings.

(e) Partner organization dispensing by mail

Women on Web (WoW), an internet group, connects patients and providers outside of the US and provides medical abortion globally, dispensing mifepristone through "a partner organization" by mail. WoW uses a model with numerous deviations from the standard provision of medical abortion in the United States. For example, this model has no synchronous interaction with the prescriber during informed consent or prior to prescribing medication and no confirmation of self-reported medical, surgical, and menstrual history or confirmed pregnancy testing. Three studies (Endler, Norten, and Aiken (2017))¹¹⁶ reported outcomes based on dispensing through this model. Endler and Norten reported outcomes from WoW cohorts but do not provide relevant information on mifepristone dispensing by mail because neither provide meaningful outcomes data for consideration. Although Aiken (2017) is a large cohort study, the outcomes are self-reported and an unusually high rate of outcomes are unaccounted for; these limitations result in the data being insufficient to determine the safety of dispensing mifepristone by mail through a partner organization.

In sum, there are insufficient data from the literature we have reviewed to determine the safety and efficacy of dispensing from a retail pharmacy, by courier, or by a partner organization. With respect to dispensing mifepristone by mail, our review of the literature indicates that dispensing mifepristone by mail from the clinic or from a mail order

¹¹⁵ Reynolds-Wright JJ, et al. BMJ Sex Reprod Health 2021;0:1–6. doi:10.1136/bmjshr-2020-200976.

¹¹⁶ Endler et al., Norten et al., and Aiken et al., supra n. 85.

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pharmacy does not appear to jeopardize the efficacy of mifepristone for medical abortion. While the studies we reviewed are not adequate on their own to establish the safety of the model of dispensing mifepristone by mail, the safety and efficacy outcomes reported in these studies remain within the ranges labeled for the approved mifepristone products. Although the literature suggests there may be more frequent ED/urgent care visits related to the use of mifepristone when dispensed by mail from the clinic, there are no apparent increases in other significant adverse events related to mifepristone use.

Based on the REMS assessment data, FAERS data from the time period when the in-person dispensing requirement was not being enforced, and our review of the literature, we conclude that mifepristone will remain safe and effective if the in-person dispensing requirement is removed, provided all the other requirements of the REMS are met and pharmacy certification is added. Removing the in-person dispensing requirement will render the REMS less burdensome to healthcare providers and patients, and provided all other requirements of the REMS are met, including the additional requirement for pharmacy certification, the REMS will continue to ensure that the benefits of mifepristone for medical abortion outweigh the risks. Therefore, to reduce the burden imposed by the Mifepristone REMS Program, the REMS must be modified to remove the in-person dispensing requirement, which would allow, for example, dispensing of mifepristone by mail via certified prescribers or pharmacies, in addition to in-person dispensing in clinics, medical offices and hospitals as currently outlined in ETASU C.

In your Petition, you state that “[e]liminating or relaxing the REMS to facilitate Internet or telephone prescriptions would be dangerous to women and adolescent girls” and that “health care providers prescribing abortion-inducing drugs over the Internet or phone or before a patient is even pregnant cannot adequately evaluate patients for contraindications to the drugs” (Petition at 18-19).

We do not agree that eliminating the REMS requirement for the dispensing of Mifeprex in certain healthcare settings will be dangerous to patients, nor do we agree that doing so will affect the ability of healthcare providers to evaluate women for contraindications to mifepristone in a regimen with misoprostol for medical termination of intrauterine pregnancy through 70 days gestation. There are many factors that contribute to patient safety, including evaluation of a patient, informed consent, development of a follow-up plan, and provision of a contact for emergency care. All of these can occur in many types of healthcare settings. The evaluation of patients for contraindications to medical abortion does not necessarily require direct physical contact with the certified prescriber.

You also assert that telemedicine abortion absolves abortion providers of responsibility for the well-being of their patients (Petition at 19). We do not agree. Healthcare providers who prescribe mifepristone are responsible for the well-being of their patients regardless of mode of evaluation or dispensing of medication. The Agency agrees with the American Medical Association that a healthcare provider-patient relationship is entered when the “physician serves a patient’s medical needs;”¹¹⁷ in the context of medical abortion, this

¹¹⁷ See www.ama-assn.org/delivering-care/ethics/patient-physician-relationships.

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healthcare provider-patient relationship continues until resolution of the pregnancy or transfer of care to another healthcare provider.¹¹⁸

We also note that patients who are not pregnant at the time of evaluation would not be appropriate candidates for being prescribed mifepristone for medical termination of pregnancy because they do not fulfill the approved indication of having an intrauterine pregnancy of up to 70 days gestation.

2. Other Safety Issues and Additional Studies

In support of your request that we retain the Mifeprex REMS, you cite the Council for International Organizations of Medical Sciences' (CIOMS) definition of "rare" to assert that because "about 1 out of 100 women" using Mifeprex and misoprostol require surgery, serious complications are common, not rare (Petition at 15-16).¹¹⁹ Although we agree that certain elements of the Mifepristone REMS Program are necessary to assure the safe use of mifepristone, we do not agree with your assertion.

In the Petition, you state that the Medication Guide improperly downplays the risks of the use of Mifeprex in a regimen with misoprostol and you cite the Medication Guide as stating "'rarely, serious and potentially life-threatening bleeding, infections, and other problems can occur following . . . medical abortion.' Specifically, 'in about 1 out of 100 women [administered Mifeprex and misoprostol] bleeding can be so heavy that it requires a surgical procedure.'" (Petition at 15). Using these two separate statements in the Medication Guide, you argue that the CIOMS's definition of rare ("1 out of 1000") means that if 1 out of 100 women using Mifeprex in a regimen with misoprostol require surgery, serious complications are common, not rare. (Petition at 16). However, your reference to the two sentences in the Medication Guide conflates two different clinical scenarios: (1) the adverse event of serious and potentially life-threatening bleeding, and (2) treatment failure.

The first sentence you reference states: "Although cramping and bleeding are an expected part of ending a pregnancy, rarely, serious and potentially life-threatening bleeding, infections, or other problems can occur following a miscarriage, surgical abortion, medical abortion, or childbirth." This statement refers to life-threatening adverse events that can occur during termination regardless of gestational age or during miscarriage or childbirth regardless of the mode of delivery (e.g., vaginal delivery or cesarean section). At the time of our review of the clinical studies submitted to support the S-020 efficacy supplement, the reported rate of death in the studies reviewed, based on one death, was 0.007 percent (very rare under the CIOMS definition).¹²⁰ The rate of infections requiring hospitalization or

¹¹⁸ See <https://www.ama-assn.org/delivering-care/ethics/ethical-practice-telemedicine>.

¹¹⁹ Council for International Organizations of Medical Sciences. Guidelines for Preparing Core Clinical Safety Information on Drugs Second Edition. 1999. <https://cioms.ch/wp-content/uploads/2018/03/Guidelines-for-Preparing-Core-Clinical-Safety-Info-Drugs-Report-of-CIOMS-Working-Group-III-and-V.pdf>. Accessed December 13, 2021 (CIOMS).

¹²⁰ Id. at 36 (defining the "very rare" standard category of frequency as less than 0.01 percent).

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intravenous antibiotics was less than 0.1 percent (rare under the CIOMS definition),¹²¹ and rates of transfusion were 0.03-0.7 percent (rare to uncommon under the CIOMS definition).¹²² Therefore, “rarely” accurately refers to the frequency of the adverse events referenced in this statement.

The second sentence you reference from the Medication Guide states: “In about 1 out of 100 women, bleeding can be so heavy that it requires a surgical procedure (surgical aspiration or D&C).” This statement refers to the rate of surgical procedures for bleeding following treatment with mifepristone. Heavy bleeding or hemorrhage after medical abortion is a small subset of bleeding and can require a surgical procedure due to ongoing pregnancy or incomplete expulsion; these are considered failed treatment rather than adverse events and are not characterized using the CIOMS definitions. Even if heavy, bleeding after medical abortion may not be considered a serious adverse event unless clinically diagnosed as hemorrhage or requiring a transfusion. Furthermore, in the vast majority of medical abortions, surgical intervention is not necessary.

You also cite a 2009 study and a 2018 study to assert that medical abortions carry greater risks than surgical abortions (Petition at 16). The 2009 Niinimäki, et al.¹²³ study reported overall incidences of immediate adverse events (up to 42 days) in medical and surgical abortions performed in women undergoing induced abortion from 2000-2006 based on data from the Finnish national registries. We agree that the overall incidence of adverse events for medical abortion was fourfold higher when compared with surgical abortion (20.0 percent versus 5.6 percent). Specifically, the incidence of hemorrhage, incomplete abortion, and surgical (re)evacuation were higher for medical abortion. However, the authors specifically noted that because medical abortion is associated with longer uterine bleeding, the high rate of events, which were pulled from a national registry reflecting both inpatient and outpatient visits, is not surprising. They opined that uterine bleeding requiring surgical evacuation probably better reflects the severity of bleeding after termination of pregnancy; the incidence of such bleeding was relatively low, although it was more common with medical abortion. In addition, the authors acknowledged there are inherent weaknesses in registry-based studies; there is variable reliability both of diagnoses and of severity of diagnoses. Nevertheless, the authors concluded that both methods are generally safe and recommended discussing the adverse event profiles of different methods when counseling women seeking pregnancy termination.

We note that Ireland, et al.¹²⁴ reported findings from a more recent retrospective cohort study of 30,146 United States women undergoing pregnancy termination before 64 days of gestation from November 2010 to August 2013. Efficacy of pregnancy termination was 99.6 percent and 99.8 percent for medical and surgical abortion, respectively.

¹²¹ Id. at 36 (defining the “rare” standard category of frequency as greater than or equal to 0.01 percent and less than 0.1 percent).

¹²² Id. at 36 (defining the “uncommon” standard category of frequency as greater than or equal to 0.1 percent and less than 1 percent); see also 2016 Clinical Review, *supra* n. 13, at 47 and 51.

¹²³ Niinimäki M, Pouta A, Bloigu A, et al. Immediate complications after medical compared with surgical termination of pregnancy. *Obstet Gynecol.* 2009;114(4):795-804.

¹²⁴ Ireland LD, Gatter, M, Chen, A. 2015. Medical Compared with Surgical Abortion for Effective Pregnancy Termination in the First Trimester. *Obstetrics & Gynecology* 126:22-28.

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Unanticipated aspiration for persistent pain, bleeding or both were 1.8 percent and 0.4 percent for medical and surgical abortion respectively. These findings are compatible with the Niinimäki study findings. There was no difference in major adverse events as defined by the authors (emergency department visit, hospitalization, uterine perforation, infection, hemorrhage requiring transfusion) between the groups. The authors conclude medical and surgical abortion before 64 days of gestation are both highly effective with low complication rates.

The 2018 Carlsson study is addressed above in section II.A.2.b.ii. of this response; as discussed above, that study showed no statistically significant difference between the overall complication rates between an “at home” and “at the hospital” abortion.¹²⁵

We acknowledge that medical abortion is known to have more days of bleeding and increased rates of incomplete abortion compared to surgical abortion. However, as noted above, in the vast majority of medical abortions, surgical intervention is not necessary. Thus, medical abortion and surgical abortion are two options; both have benefits, side effects, and potential complications. Patients and their healthcare providers should discuss which method is preferable and safer according to each woman’s unique situation.

You state that the Mifeprex REMS should require a formal study for at-risk populations, including: patients under the age of 18; patients with repeat Mifeprex abortions; patients with limited access to emergency room services; and patients who self-administer misoprostol (Petition at 13-14). As we explain below, additional studies are not needed at this time.

In justifying your assertion that a formal study is required in patients under the age of 18, you state that Mifeprex was approved for use in the pediatric population in 2000 after the requirement for studies in the pediatric population was waived (Petition at 13-14). The approved indication for mifepristone does not limit its use by age. Although patients age 17 and under were not included in the clinical trials supporting the initial approval of Mifeprex in 2000, we stated at the time that the safety and efficacy were expected to be the same for postpubertal (i.e., post-menarchal) adolescents. Our conclusion in 2000 that pediatric studies of Mifeprex were not needed for approval was consistent with FDA’s implementation of the regulations in effect at that time. Because we determined that there were sufficient data from studies of mifepristone, the original Mifeprex approval should have reflected the Agency’s conclusion that the pediatric study requirements were waived for pre-menarchal females and that the pediatric study requirements were met for post-menarchal adolescents, rather than stating that the Agency was waiving the requirements for all pediatric age groups.

As currently required by the Pediatric Research Equity Act (PREA),¹²⁶ certain applications or supplemental applications must include pediatric assessments of the safety and effectiveness of the drug for the claimed indication(s) in all relevant pediatric

¹²⁵ Carlsson et al., *supra* n. 49.

¹²⁶ Section 505B of the FD&C Act (21 U.S.C. 355c).

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subpopulations, unless that requirement is waived or deferred.¹²⁷ In accordance with PREA, when FDA reviewed the S-020 efficacy supplement, a partial waiver was granted for pediatric studies in pre-menarchal females because pregnancy does not occur in premenarchal females. We also determined that the applicant had fulfilled the pediatric study requirement in post-menarchal adolescents. This determination was based on data extrapolated from adults and information in literature. Review of these findings found the safety and efficacy in this population to be similar to the safety and efficacy in the adult population.¹²⁸ Therefore, we do not agree that a formal study is required in patients under 18.

With regard to your concerns about repeat abortions and your assertion that a study is necessary in this population, we acknowledge that published data concerning adverse reproductive health outcomes in U.S. women who undergo repeat medical abortions are limited. We concluded in our 2016 review of the S-020 efficacy supplement that there is no evidence that repeated medical or surgical abortion is unsafe or that there is a tolerance effect. We also noted that return to fertility after the use of mifepristone is well documented.¹²⁹ This is reflected both in Section 17 of the approved labeling, Patient Counseling Information, which states that the provider should “inform the patient that another pregnancy can occur following medical abortion and before resumption of normal menses,” and in the Medication Guide, which states “You can become pregnant again right after your pregnancy ends.” Although you state that more than one out of every three abortions in the United States is a repeat abortion (Petition at 14),¹³⁰ we are not aware of reports suggesting greater safety concerns in repeat abortions than a first-time abortion. Therefore, we do not agree that a study is necessary in this population. You also cite a published study, using a mouse model, of repeated medical termination of pregnancy that showed repeat medical abortion impaired the reproductive function of female mice (Petition at 14).¹³¹ Per our 2016 review, there is no evidence in available clinical data that repeated medical or surgical abortion is unsafe, or that fertility is impaired by the use of mifepristone; therefore, data from a single non-clinical study in mice are not persuasive.¹³²

With respect to your request for a formal study of mifepristone for medical abortion in women without access to emergency care, we disagree that such a study is necessary. In order to become a certified prescriber, a healthcare provider must agree that they have the ability to provide surgical intervention in cases of incomplete abortion or severe bleeding or have made plans to provide such care through others, and that they have the ability to assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if necessary. These prescriber qualifications ensure that mifepristone is prescribed to women for whom emergency care is available.

¹²⁷ Section 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(2)).

¹²⁸ 2016 Clinical Review, *supra* n. 13, at 74-76.

¹²⁹ *Id.* at 47.

¹³⁰ In support of this assertion, you cite Jones R, Jerman J, Ingerick M. Which abortion patients have had a prior abortion? Findings from the 2014 U.S. Abortion Patient Survey. *J Womens Health*.

¹³¹ Lv F, Xu X, Zhang S, et al. Repeated abortion affects subsequent pregnancy outcomes in BALB/c mice. *PLoS One*. 2012;7(10):e48384. doi:10.1371/journal.pone.0048384.

¹³² 2016 Clinical Review, *supra* n. 13, at 47.

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Finally, you assert that FDA should require a formal study in patients who self-administer misoprostol. As explained in section II.A.2.b.ii of this response, FDA conducted a literature review of self-administration of misoprostol at home as part of its review of the S-020 efficacy supplement and found no safety or efficacy concerns with home self-administration of misoprostol. Therefore, we disagree that a formal study is required in this population.

With regard to safety generally, in addition to the FAERS data provided above (see section II.B.1.c.ii. in this response), FDA routinely monitors adverse events reported to FAERS and published in the medical literature for mifepristone for medical termination of pregnancy through 70 days gestation. We have not identified any new safety concerns with the use of mifepristone for this indication.

3. Other Articles

In your Petition, you reference several documents that discuss alternative models of providing abortion medications and advocate for the lifting of the REMS on mifepristone (Petition at 23-24). You assert that these recent publications demonstrate how abortion advocates will continue to pressure FDA to eliminate the REMS and move towards over-the-counter access for Mifeprex.¹³³

We agree that the overarching message in the publications you reference appears to be advocating self-management of medical abortion. Nonetheless, as discussed in this response, we have determined that the Mifepristone REMS Program continues to be necessary for the safe use of this drug product, with some modifications.

III. CONCLUSION

For the reasons set forth above, we deny your request that FDA restore and strengthen elements of the Mifeprex regimen and prescriber requirements approved in 2000; and we grant in part and deny in part your request to retain the Mifepristone REMS Program. As with all approved drug products, we will continue to monitor the safety of mifepristone for the approved indication and take any appropriate actions.

Sincerely,

Patrizia A.
Cavazzoni -S

Digitally signed by Patrizia A.
Cavazzoni -S
Date: 2021.12.16 15:05:41 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

¹³³ You also reference clinical trials relating to the use of mifepristone for spontaneous miscarriage management and question the results of studies related to this use (Petition at 16-18). The use of mifepristone for the management of early miscarriage is not an approved indication for this drug product and is outside the scope of the Mifepristone REMS Program. Therefore, we do not address it in this response.